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The Electroencephalogram in Diffuse Encephalopathies

Stanley Lesse, Paul F. A. Hoefer, and James H. Austin

Experimental Study of Distant Effects of Acute Focal Brain Injury

Warren H. Kempinsky

Relationship Between Anticoagulants and Hemorrhagic Cerebral Infarction in Experimental Animals

Matthew W. Wood, Khalil G. Wakim, George P. Sayre, Clark H. Millikan, and Jack P. Whisnant

Obituary: Gilbert Horrax, M.D.

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H. E. King

Relation of Emotional Responses and Changes in Plasma Hydrocortisone Level After Stressful Interview

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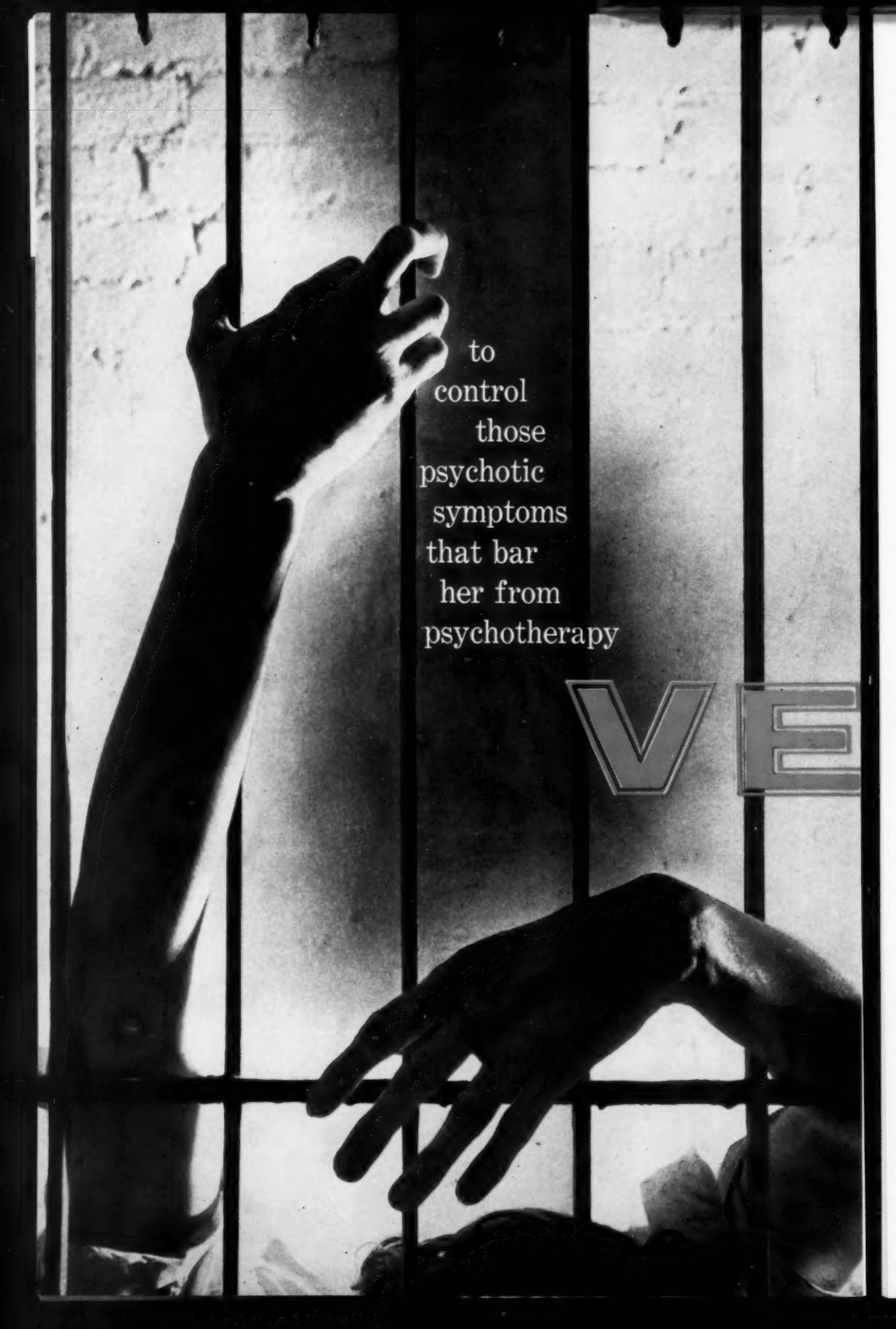
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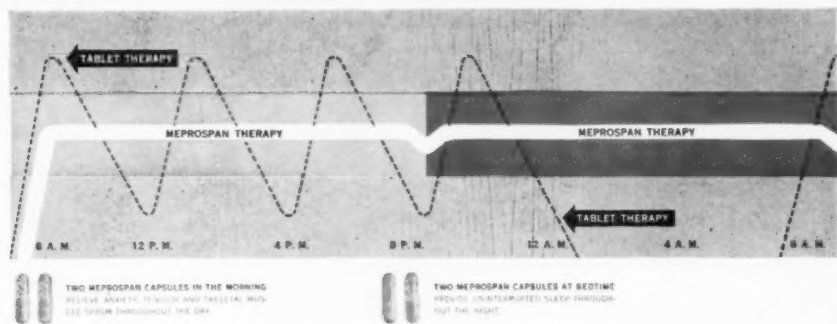
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1. Sainz, A.: Personal communication.
2. Hutchinson, J. T.: Evaluation of Pacatal in Psychotic States, address before the American Psychiatric Association, Nov. 16, 1956.
3. Bowes, H. A.: *Am. J. Psychiat.* 113:530 (Dec.) 1956.

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SECTION ON NEUROLOGY

The Electroencephalogram in Diffuse Encephalopathies

Significance of Periodic Synchronous Discharges

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Introduction

This report deals with clinical and laboratory findings in a group of 11 patients who were seen at the Neurological Institute between 1950 and 1956. The patients, all of whom suffered from encephalopathies, had in common distinctive abnormalities in the electroencephalogram (EEG), namely, periodic synchronous bursts of high-amplitude slow-wave activity, at times irregular in pattern but usually with spike-and-wave-like components. The bursts in most instances lasted for a few seconds and recurred periodically every 5 to 10 seconds. Between these bursts depressed activity was seen.

The underlying illnesses represent a wide range of etiologies, apparently unrelated. The clinical course and final outcome also varied widely. Upon analysis of the clinical features, however, a number of similarities among the cases were found, namely, "organic" mental impairment, myoclonic seizures and generalized convulsions, choreo-athetoid dyskinesia, and rigidity. While all these features did not occur in all cases,

most of them were present at the height of illness.

The possibility of a relationship of encephalopathy and changes in the EEG was first brought to our attention in 1950, when we studied a case of subacute inclusion body encephalitis of the Dawson type (Case 1). Shortly before that time Radermecker¹ and Cobb and Hill² had reported periodic synchronous bursts of abnormal slow-wave activity in the EEG as pathognomonic of subacute leukoencephalitis of the van Bogaert and Dawson varieties.

During the following years we saw identical electrical patterns in the records of 10 additional cases (Table).

Clinical Material and Electroencephalographic Findings

CASE 1.—A 15-year-old white right-handed student was well until early in February, 1951. At this time he appeared disoriented, drowsy, and "mentally sluggish." After a few days he became grossly ataxic and "held his head arched backward." A few days later he was out of contact with his environment, his speech became unintelligible, he lost sphincter control and was unable to sit up in bed. Several lumbar punctures performed during the first month of illness revealed normal pressure, protein varying from 60 to 70 mg. per 100 cc., and white cell counts—all lymphocytes—ranging from 6-15 per cubic millimeter.

He was admitted to the Neurological Institute three months after onset of illness. On admission the vital signs were normal. The patient was out of contact with his environment. There was a marked scoliosis to the right, the head also being

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Clinical Data in Eleven Cases of Diffuse Encephalopathy

No.	Age, Yr.	Sex	Diagnosis	"Organic" Mental Reactions	Seizures		Rigidity	Dyskinesia	Duration and Outcome
					Grand Mal	Myoclonic			
1	15	M	Subacute inclusion body enceph.	+	—	+	+	+	8 mo. Died; necropsy
2	59	F	Herpes simplex enceph.	+	—	+	+	+	10 days Died; necropsy
3	8	M	Infectious mononucleosis enceph.	+	+	—	+	—	3 wk. Recovered
4	16	M	Enceph., etiology unknown	+	+	+	+	+	8 days Recovered
5	3½	F	Enceph., etiology unknown	+	+	—	—	+	23 days Behavior problem
6	17	M	Myoclonus epilepsy	+	+	+	—	—	2 yr. Process advancing
7	16	F	Myoclonus epilepsy	+	+	+	—	+	4 yr. Process advancing
8	24	M	Myoclonus epilepsy	+	+	+	—	—	10 yr. Process advancing
9	11 mo.	M	Cerebral maldevelop- ment	+	+	+	+	+	From birth Process advancing
10	56	F	Diffuse encephalo- malacia	+	—	+	+	+	3 mo. Died; necropsy
11	47	F	Jakob- Creutzfeldt syndrome	+	+	+	+	+	1 yr. Died; necropsy

severely arched to the right and backward. His right upper extremity was sharply flexed at all joints and adducted against the thorax. The left upper limb was postured in a similar fashion but to a less severe degree. Both lower extremities were held widely abducted, externally rotated, and sharply flexed at all joints. The mouth was wide open at all times. He had a grimace suggestive of risus sardonicus and moaned frequently. Involuntary movements, severer on the right, were noted at approximately five-second intervals. They consisted of myoclonic jerks, hyperflexion of the forearms on the arms, bilateral dorsiflexion of the great toe, momentary stiffening and extension of the lower limbs, and paroxysmal jerking of the eyes to the right. At times, particularly when he was disturbed, gross choreoathetotic movements were noted, again more pronounced on the right. Hyperextension of the back and scoliosis were fixed and did not change when the patient was in a prone position, supported only on his abdomen and thorax. When he was lifted to a standing position, the left lower limb was rigidly locked. In spite of marked rigidity, the patient moved all limbs in response to pain. Deep tendon reflexes were normal in the upper and hyperactive in the lower limbs, the increased responses being more marked on the right. Superficial reflexes could not be elicited. Sensory modalities other than pain could not be tested. It could not be determined whether the patient could hear or see. No nystagmus or external ophthalmoplegias were noted. Corneal reflexes were active bilaterally. The patient was able to swallow.

Several blood counts and repeated studies of blood chemistry were all within normal limits. Spinal fluid studies on five separate occasions showed normal pressure. The total protein ranged from 27 to 78 mg. per 100 cc., with abnormally high γ -globulin fractions of 20% to 37%. Cell counts were all normal; the Kolmer test was negative, but on two occasions a "first-zone" colloidal gold curve was found. All x-ray studies were unremarkable. Electrocardiography revealed initially auricular tachycardia and, terminally, evidence of myocardial ischemia.

Three weeks after admission a right frontal trephination with biopsy of the right frontal lobe was performed, the operative procedure causing no apparent change in the patient's status. Gross and microscopic studies revealed a mild, diffuse, chronic inflammatory process involving the cerebral gray and white matter. It was felt that these changes were only the marginal aspects of a process that was more intense in other parts of the cortex and white matter. The diagnostic impression from the biopsy specimen was "encephalitis, type undetermined."

Numerous electroencephalograms were obtained during his stay at the hospital. All showed a highly characteristic pattern. In order to determine whether or not the bursts were movement artifacts, due to the myoclonic movements, or genuine paroxysmal discharges, combined EEG and electromyographic recordings were performed prior to, during, and after thiopental (Pentothal) sodium anesthesia (Fig. 1).

ELECTROENCEPHALOGRAPH IN DIFFUSE ENCEPHALOPATHIES

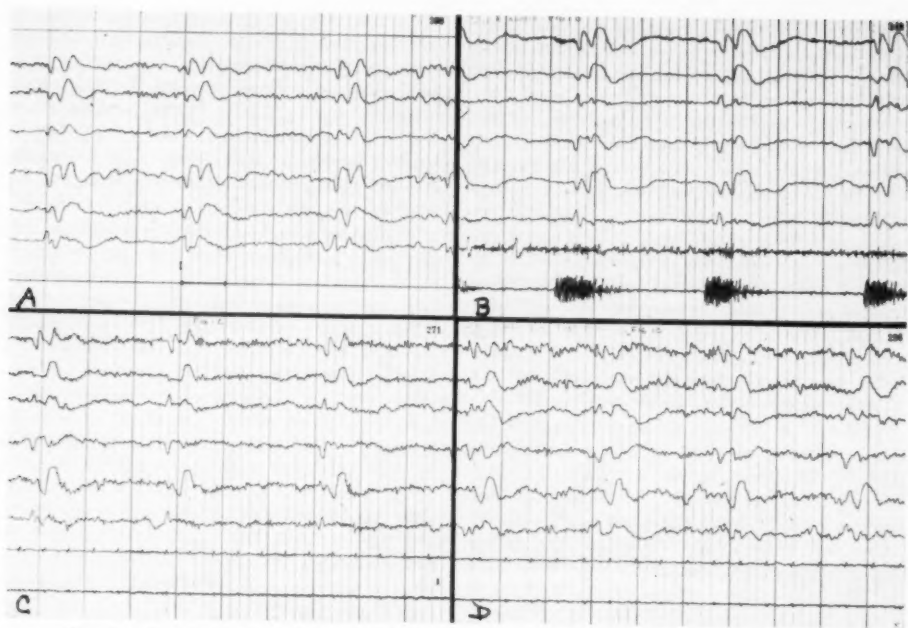


Fig. 1.—A, electroencephalogram in bipolar leads.

1, right prefrontal-right motor area; 2, right motor-right parietal area; 3, right parietal-right occipital area; 4, left prefrontal-left motor area; 5, left motor-left parietal area; 6, left parietal-left occipital area.

B-D, electroencephalogram, as in A. Electromyograms in surface leads. 7, left deltoid; 8, left extensor digitorum communis.

Calibration=50 μ v. Time=one second.

Four strips from these observations are shown. In Figure 1A the EEG pattern prior to anesthesia is seen. It consists of synchronous bursts of somewhat irregular medium- to high-voltage 2-3 cps wave activity, lasting for about a second and recurring periodically about 18 to 20 times per minute.

In Figure 1B simultaneous EEG and muscle action potential recordings (left deltoid and extensor group of the left forearm) are shown. The bursts of muscle action potentials are synchronous with or precede by a fraction of a second those in the EEG.

Figure 1C represents the same setting after intravenous injection of 7 cc. of a standard thiopental sodium solution. At this time the corneal reflexes were abolished; the muscle action potentials have almost disappeared. The heart rate is 108 a minute. The EEG is unchanged except for the presence of low-voltage rapid activity, presumably due to the barbiturate.

Figure 1D represents the state after 11 cc. of thiopental sodium. The muscle activity is now completely abolished; the EEG shows no significant change.

The patient's course was progressively downhill, and he died seven and a half months after the onset of his illness. During the last month of his life he ran a fever of 100-102 F. Occasional episodes of paroxysmal tachycardia were noted. Moderate hyperpnea was present during the last month of life. The patient was treated intensively with various antibiotics and anticonvulsants. Shortly after his admission tube feeding was started. Despite this, he steadily lost weight. He was incontinent of urine throughout his hospitalization.

The myoclonic movements were less frequent when the patient was undisturbed. During sleep the choreiform and myoclonic movements alike were greatly diminished in frequency and intensity, but not abolished at first. After several months the abnormal movements occurred less frequently and ceased during sleep.

As the illness progressed, the athetoid elements to the movements became more prominent, particularly in the left upper limb. The fingers of the left hand gradually closed to form a clenched fist. Repeated testing revealed that the patient was blind at that time. No spontaneous involuntary

movements were noted during the last month, and relatively little motor response was noted on stimulation. He died in cardiovascular collapse with pulmonary edema.

Necropsy.—Postmortem findings were consistent with the diagnosis of subacute inclusion body encephalitis (Dawson type) with diffuse involvement of the cortex, subcortical white matter, basal ganglia, thalamus, and brain stem. The cerebellum and spinal cord were involved but to a less degree than the above-mentioned structures. A slight degree of perivascular lymphocytic inflammatory reaction was present. Intranuclear eosinophilic inclusion bodies were seen, occasionally associated with cytoplasmic inclusion bodies. These inclusion bodies were found in degenerating nerve cells and, to a less extent, in the oligodendroglia.

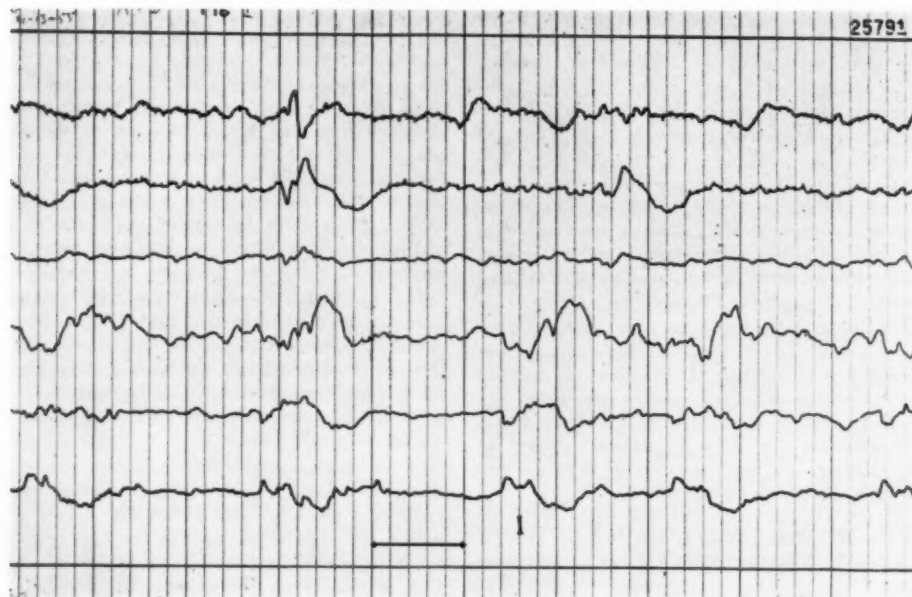
CASE 2.—A 59-year-old right-handed Negro woman was well until four days prior to admission to the Neurological Institute of New York, when she began to complain of frontal and occipital headache and shortly afterward of drowsiness. Three days prior to admission, she vomited and had an elevated temperature. At the same time, she was very restless and anorexic, experienced general malaise, and complained of midlumbar back pain. On the day prior to admission, she was confused and had visual hallucinations.

On admission the temperature was 103 F, pulse 100, respirations 18, and blood pressure 160/70. Neurological examination revealed constant grimacing and choreiform movements of all limbs, more marked on the left. There was no weakness, and reflexes were normal. No cranial nerve or sensory deficits could be elicited. The patient was disoriented in all spheres, confabulated, and had fragmentation of speech.

Two white blood cell counts were 8400 and 9400 per cubic millimeter, with 90% and 70% polymorphonuclear cells, respectively. Sedimentation rates ranged from 10 to 25 mm. in one hour. The blood Mazzini test was negative. Blood chemistry values and heterophil antigen agglutination titer were all within normal limits. X-rays of the skull, chest, spine, and abdomen were all negative. Three lumbar punctures were performed. All revealed normal pressure. On admission the cell count was 90 white cells per cubic millimeter, all lymphocytes. Two days later the count rose to 200 cells, with 91% lymphocytes, and the protein was 80 mg. per 100 cc. Four days later the count rose to 270 white cells, with 89% lymphocytes, and the protein was 240 mg. per 100 cc. Cerebrospinal fluid sugars were within normal range. Serology, bacterial culture, and virus studies were negative. The electroencephalogram on the second hospital

Fig. 2.—1, right prefrontal-right anterior temporal area; 2, right anterior-right posterior temporal area; 3, right posterior temporal-right occipital area; 4, left prefrontal-left anterior temporal area; 5, left anterior-left posterior temporal area; 6, left posterior temporal-left occipital area.

Calibration=50 μ v. Time=one second.



ELECTROENCEPHALOGRAM IN DIFFUSE ENCEPHALOPATHIES

day was grossly abnormal. Six days later (Fig. 2) the record showed periodic recurrent bursts of slow-wave activity of medium- to high-amplitude (2-5 cps). The periodicity was every three to four seconds.

The temperature ranged from 99 to 104.5 F. Initially, there appeared to be some fluctuation in her mental picture, with short periods of clarity. The general status became gradually worse. The choreiform movements were present for the first six days. During this period they gradually increased in severity, being most marked when the temperature was elevated. At times myoclonic jerking of all limbs was noted. Roving eye movements and bilateral grasp reflexes appeared. There was a gradual development of generalized muscle rigidity. On the sixth hospital day, all movements ceased, but the rigidity remained. At this time the patient was comatose. She remained in coma until her death, in respiratory failure on the 10th hospital day.

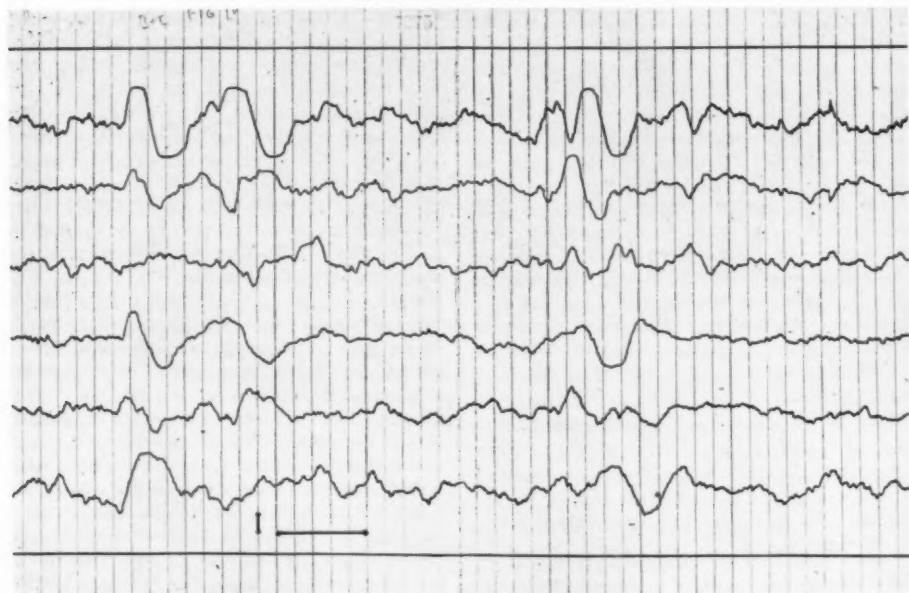
Necropsy.—The diagnosis was herpes simplex encephalitis. This was characterized by widespread necrotizing inflammatory lesions of the cortex and white matter with less extensive involvement of the basal ganglia, thalamus, and brain stem, and almost no involvement of the cerebellum. Small numbers of intranuclear eosinophilic inclusions were seen in the nerve cells and oligodendroglia.

CASE 3.—An 8-year-old white boy developed a sore throat and swelling of the left anterior cer-

vical lymph nodes two weeks prior to admission to the Neurological Institute. Two days prior to his admission he had a headache and fever (103 F), chills, and vomiting. Examination revealed an enlarged, tender spleen. He became confused and irritable. During a lumbar puncture he became cyanotic and had a right-sided seizure. In spite of parenteral barbiturate medication, he had several additional convulsions. His temperature rose to almost 104 F and he became comatose. There was a leukocytosis (25,600 cells), with 68% polymorphonuclear leukocytes and 32% lymphocytes. Lumbar puncture revealed normal pressure and cell count. The protein was 256 mg. per 100 cc. He was transferred to the Neurological Institute that same day.

At the time of admission, the patient was restless and semicomatose. The temperature was normal; pulse 116/min.; respiration 28/min. General examination revealed cervical lymphadenopathy, a moderately injected pharynx, and a palpable spleen. The child did not respond to auditory stimuli. He did move all limbs in response to pain. Slight nuchal rigidity was present. Muscle tonus appeared to be increased at times, while the deep tendon reflexes were bilaterally active and equal, with a bilateral Babinski sign. On cranial nerve examination, inconstant deviations of either eye alone were noted. White blood cell counts were in the high normal range. Lymphocyte counts varied from 32% to 25% during the first five days. On the sixth day 67% lymphocytes were found.

Fig. 3.—Same as Figure 1A.



Abnormal lymphocytes were recorded on two occasions. Heterophil antigen agglutination titers were 1:1024 on the second hospital day* and on two other occasions. Six weeks after discharge from the hospital the titer was 1:16. Three lumbar punctures showed normal pressure. Pleocytosis, with a count of 21, was seen on the second hospital day, and the protein was 148 mg. per 100 cc. Eight days later the cell count was normal, but the protein had risen to 178 mg. per 100 cc. Six weeks after discharge all findings were normal. Serological tests for the commoner viral encephalitis were negative.

The electroencephalogram (Fig. 3, taken on the third hospital day) (temperature 105 F) consisted at times of synchronous periodic bursts of high-voltage 1-2 cps wave activity against a background of disorganized low-voltage 5-7 cps and low-voltage rapid activity. Periodic bursts recurred every five seconds. Two weeks later, when he had almost recovered, periodicity in the EEG was still noted on a few occasions. Eighteen months later, the record basically was mildly abnormal without periodicity, and synchronous bursts of high-voltage 3-4 cps activity were seen with hyperventilation.

The diagnosis of encephalitis due to infectious mononucleosis was made. During the next few days the temperature ranged from 99.5 to 105 F. He was irritable and disoriented in all spheres. Several left-sided seizures occurred, followed by opisthotonos and unconsciousness. On the fourth hospital day, the temperature was near normal, and the patient was alert and neurologically normal aside from slight nuchal rigidity. On the fifth day the temperature rose again to 106.7 F, and the patient lost consciousness and went into opisthotonos, with all limbs rigidly extended. Extensor plantar responses were again recorded. During the following 48 hours the temperature dropped gradually. On the eighth hospital day he was conscious but still disoriented for time. Rigidity and abnormal reflexes persisted, as well as incontinence. By the 11th day the mental status had cleared and the motor abnormalities subsided. The patient was discharged on the 19th hospital day. During a six months' follow-up, the only abnormality observed was slight intention tremor in the finger-to-nose test on the left. When he was finally seen, after another year, he had completely recovered.

CASE 4.—A 16-year-old right-handed student was well until two days prior to admission to the Neurological Institute of New York. He was said to have had "some difficulties in playing basketball" and one hour later had a generalized tonic-

clonic seizure with urinary incontinence but without focal or lateralizing signs. He was admitted to a hospital, where the temperature was recorded at 103 F. He was said to have had abnormal movements. He had leukocytosis (13,000 per cubic millimeter) and a normal spinal fluid pressure and cell count, with a protein of 62 mg. per 100 cc. On the next day he was alert and afebrile. On the following day a second grand mal seizure occurred. The temperature rose to 104 F on this occasion, and again abnormal movements were observed. Six hours later the patient was admitted to the Neurological Institute.

The temperature on admission was 104 F, pulse 100/min., respiration 24/min., and blood pressure 115/70 mm. Hg. The patient was comatose but very restless. On neurological examination, nuchal rigidity was found by some observers. In addition to the generalized restlessness, choreoathetotic movements were seen in all extremities. Also, twitching of large bundles of muscle fibers were seen in all limbs. Some of the movements were myoclonic in character. External stimuli did not seem to influence the movements. No gross motor weakness was evident, and there were no significant abnormalities of reflexes or muscle tone. No clear-cut sensory deficits could be elicited, and as far as could be determined the cranial nerves were intact.

White blood cell counts were as high as 13,000 per cubic millimeter on two occasions, with 12% monocytes on one occasion and polymorphonuclear cell counts ranging from 67% to 94%. No atypical cells were recorded after special examinations. Repeated spinal fluid studies revealed no abnormalities. Bacterial and viral studies of spinal fluid and blood were negative. Heterophil antigen titers were normal on two occasions.

Electroencephalograms were recorded on six occasions during the next two months. The first one (Fig. 4A), on the morning after admission, showed extremely slow activity, ranging from $\frac{1}{2}$ to 2 cps in periodic bursts, recurring every few seconds. At times the bursts showed an atypical spike-and-wave pattern. Depressed activity was found between the bursts.

The second record, two days after admission (Fig. 4B) showed again periodic slow-wave bursts, which were somewhat higher in amplitude, ranged from 2-3 cps, and recurred every five seconds. On both occasions the temperature was 103 F, and the patient was in coma. At the time of the first record, the patient showed choreoathetoid movements; there were none at the time of the second.

The records remained abnormal for another two weeks, but periodic bursts were found only on a few occasions, on the 9th and 16th hospital days. Two months after the onset of illness the record was normal.

* Significant titers in our laboratory are 1:128 and above.

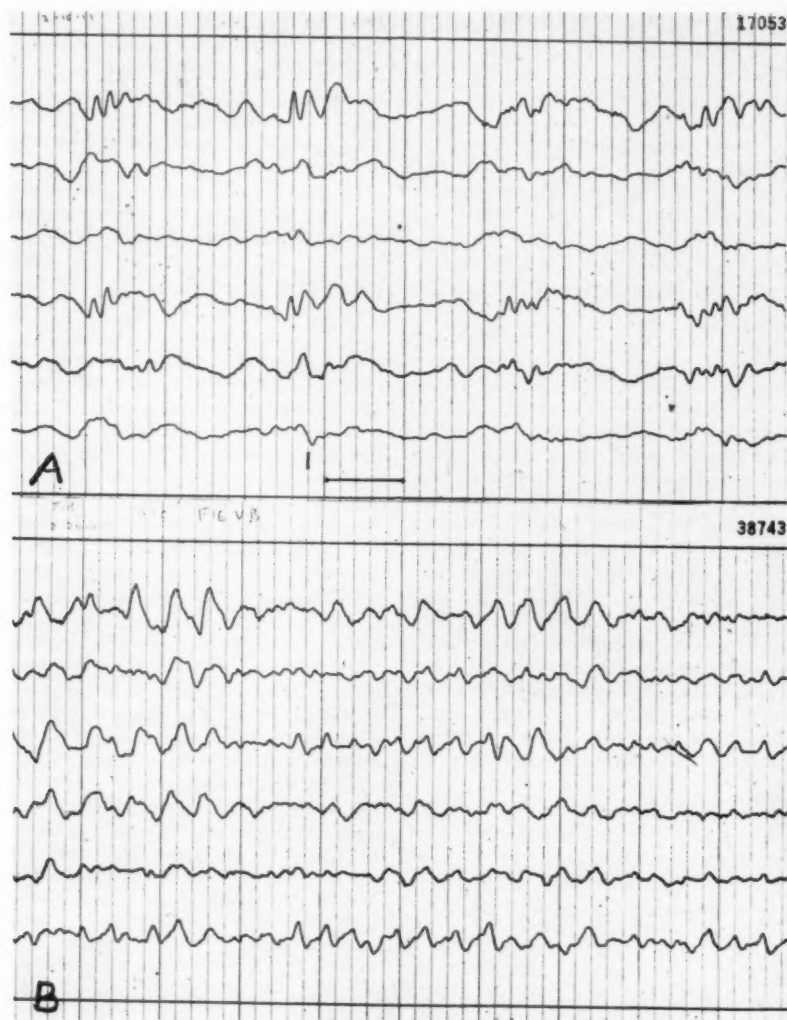


Fig. 4.—Same as Figure 1A.

On the day of admission the temperature rose to 106.5 F. It fell to 103 F the next morning. At that time the patient was comatose. The choreo-athetoid movements were no longer present on the second day after admission, but gross fasciculations were seen in all extremities. The upper and lower limbs were maintained in flexion with moderate rigidity, especially in the lower limbs, the rigidity being perhaps a little more pronounced on the left. Tonic neck reflexes were not obtained. He had unsustained patellar clonus bilaterally, while all other deep tendon reflexes were hypoactive.

During the next two days the temperature fell gradually to 99 F and remained normal after this.

He gradually became more alert, and 48 hours after admission he responded to questions for the first time but revealed psychotic manifestations, such as frightening visual hallucinations and disorientation as to time and place. These manifestations cleared after four days. By the time his temperature became normal his abnormal movements had ceased. By the sixth hospital day the patient was symptom-free. He was discharged about two weeks later on a regime of diphenylhydantoin (Dilantin) sodium 0.1 gm. t. i. d. He has been seen as an outpatient on several occasions over a period of six months and has remained free

of symptoms. The discharge diagnosis was encephalitis of unknown etiology.

CASE 5.—A 3½-year-old girl was well until one month prior to admission to the Neurological Institute, when she began to vomit spontaneously, without other abnormalities. Three days later, after a period of lethargy and irritability, she lost consciousness and had two grand mal seizures followed by confusion and disorientation, lasting eight days.

Two weeks prior to admission she again became lethargic and irritable. She was ataxic, tending to veer to the left, and her left lower limb appeared weak. Eleven days prior to admission, tremor and incoordination of the left upper limb appeared. One week prior to admission, fever developed, the temperature ranging from 101 to 104 F. The leukocyte count was 29,000 per cubic millimeter. Blood and urine cultures and a spinal fluid examination, performed in another hospital, were normal. On treatment with antibiotics, the temperature returned to normal. However, four days prior to admission the ataxia increased, so that she was unable to stand or walk and was unsteady even when sitting. Tremors of both upper limbs were noted.

The child was very lethargic and irritable. Neurological examination on admission revealed marked truncal ataxia. She was unable to stand or walk. There was marked ataxia of both upper limbs, with bilateral intention tremor. Reflexes were hyperactive bilaterally, with sustained ankle clonus.

The sedimentation rate was 40 mm. in one hour. Cerebrospinal fluid studies revealed 115 white cells per cubic millimeter (all lymphocytes). Protein and sugar values were normal, and cultures were negative. The Mantoux test (1:10,000) was nega-

tive; the heterophil agglutination titer, normal. Viral complement-fixation studies were negative.

An electroencephalogram taken on the day after admission showed gross abnormalities. These consisted of high-voltage slow-wave runs at rates of 1-4 cps, at times being a little more pronounced on the right (Fig. 5).

Three weeks later, when she was clinically much improved, a repeat EEG showed periodic bursts of medium- to high-voltage 3-4 cps activity, irregularly recurring every three to five seconds, synchronously in all leads and without much difference between the two sides.

The patient improved slowly. At the time of discharge, after 21 days in the hospital, there were still slight truncal swaying and slight intention tremor, more marked on the left. The child was irritable throughout this course. The discharge diagnosis was encephalitis, etiology unknown. On subsequent examinations it was found that all signs of ataxia and tremor had disappeared, but the child continued to be a "behavior problem."

CASE 6.—A youth, aged 17, was well until two years prior to admission to the Neurological Institute, when he had a period of unconsciousness lasting one-half hour. Later the same day he developed a temperature of 104 F, which persisted for several days. During this period he was disoriented, confused, and mute most of the time; he also had "jerking movements of the arms and legs." As his temperature gradually fell to normal, confusion and abnormal movements abated; however, he developed jaundice, which lasted five days. A diagnosis of infectious hepatitis was made. During the following year occasional "jerking" movements of his arms were noted. Fourteen months prior to admission, he had a grand mal seizure, and, in spite of various anticonvulsant

Fig. 5.—Same as Figure 2.

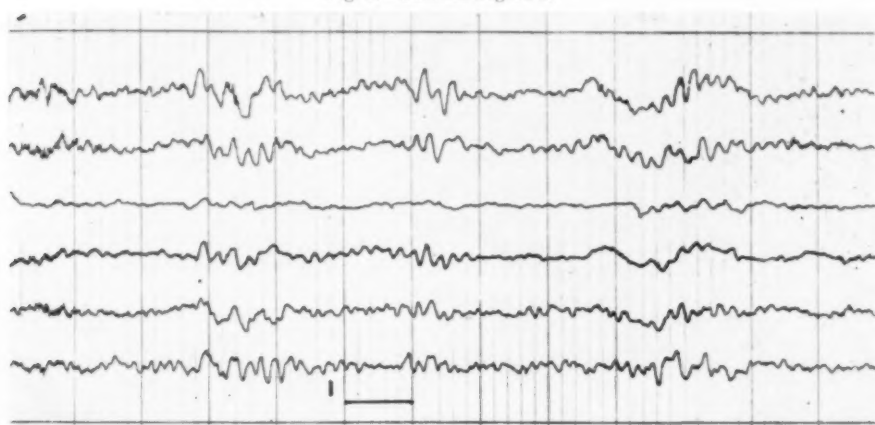




Fig. 6.—1, right motor-right anterior temporal area; 2, right anterior temporal-right prefrontal area; 3, right prefrontal-right motor area; 4, left motor-left anterior temporal area; 5, left anterior temporal-left prefrontal area; 6, left prefrontal-left motor area.

medicaments, he continued to have seizures every one to four weeks. After a reportedly normal pneumoencephalogram, eight months prior to admission, the seizures began to occur several times per week. Five months prior to admission he began to have poor motor coordination and impairment of vision. Speech became halting, and his use of words was often incorrect. He was unable to concentrate. All symptoms became progressively worse.

The family history was relevant in that the parents were first cousins and that a younger brother had a history of seizures.

On admission the patient was lethargic, dysarthric, and mentally retarded. He was unable to walk without support, and there was marked ataxia of all extremities. Reflexes were hyperactive. Eye movements appeared dissociated, and marked nystagmus was noted on lateral gaze.

All laboratory studies were unremarkable except for EEG findings and psychological testing. The latter showed evidence of intellectual impairment secondary to organic brain disease.

The EEG record (Fig. 6) consisted chiefly of recurrent synchronous bursts of medium- to high-voltage 3-4 cps wave and abortive spike-and-wave activity in all leads, but with a bifrontal preponderance. On a few occasions, more clearly

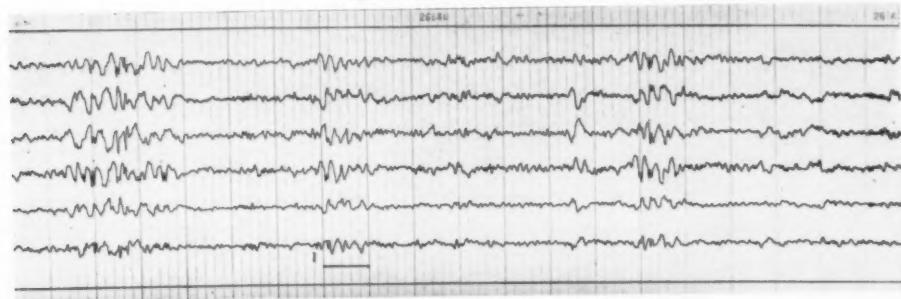
marked spike groups and spike discharges without the wave component were seen, especially in the frontal and temporal areas. The bursts recurred every few seconds, and the activity between bursts was depressed. There was no normal activity present.

The patient had at first frequent grand mal seizures and, in addition, episodes of myoclonic twitching of all limbs and of the head and neck. Some paranoid delusions accompanied by visual hallucinations were recorded on several occasions. Gradually, the seizures were brought under better control. The patient was discharged after 20 days with the diagnosis of myoclonus epilepsy.

CASE 7.—A 16-year-old girl was well until the age of 10 years, when she was noted to "twitch" slightly in her sleep, especially in response to noises. At the age of 11, she fell on several occasions without apparent cause. At 12 years, she had her first grand mal seizure. In spite of anticonvulsant medication, she continued to have nocturnal grand mal seizures. During the waking period, marked generalized "twitchings" were noted. These became so severe that she was unable to walk without support.

She was the first of nonidentical twins. Her birth weight was 4 lb., 8 oz. (2039 gm.). The twin died shortly after birth. Initially, she had

Fig. 7.—Same as Figure 6



some breathing difficulty and was placed in an incubator for two weeks. She did not walk until 18 months of age.

Examination on admission was unremarkable except for generalized, unorganized, nonrhythmic contractions of small and large groups of muscle bundles, which were accentuated by attempts to perform purposeful acts. Tests, including lumbar puncture, pneumoencephalography, and arteriography, were unremarkable.

The EEG record (Fig. 7) consisted basically of low-voltage, mildly disorganized activity, interrupted every few seconds by synchronous bursts of mostly high-voltage multispike and spike-and-wave activity, lasting one to two seconds at a time. These bursts were often, but not always, associated with myoclonic jerks.

The diagnosis of myoclonus epilepsy was made. Both the grand mal seizures and the myoclonic jerking were improved after trial with many different anticonvulsants, and the patient was discharged after one month.

Improvement, however, was maintained for a few months only. Gradually her difficulties increased; she has required several additional hospitalizations in an attempt to control seizures and abnormal movements.

Psychometric studies showed a full-scale intelligence quotient of 66, while 18 months earlier it had been 72. Her over-all scores were indicative of cerebral pathology.

CASE 8—A 24-year-old college student was first seen at the Neurological Institute in 1954. The diagnosis was myoclonus epilepsy associated with cortical and cerebellar degeneration. This patient had had a severe head trauma at the age of 11. Three years later he had an episode of confusion followed by paralysis of the left upper limb, lasting about six hours. Since the age of 16 he had had a total of four grand mal attacks, but had had daily episodes of "black-out spells" with jerking

movements of the head, often precipitated by passing from a sunny to a dark area. Since the age of 20, he had had slurred speech, unsteadiness of gait, and clumsiness of movements of the right upper limb, and more recently spontaneous jerking movements of both upper limbs. During the past year and a half he had had a number of episodes during which he lost consciousness and fell to the floor, without convulsive movements.

Neurological examination revealed slight dysarthria, dragging of the right leg, slight tremor on finger-to-nose test bilaterally, and incoordination of the right hand. The left optic disk showed atrophy.

The pneumoencephalogram revealed slight cortical atrophy on the left.

The EEG (Fig. 8) was basically disorganized, with short bursts of medium- to high-voltage 3 cps wave activity, appearing simultaneously on the two sides. Bursts of 3 cps spike-and-wave activity were at times seen synchronously on the two sides. The slow-wave bursts were brought out especially with hyperventilation and recurred in slightly irregular periods every six to eight seconds. All abnormal features were a little more marked on the left side. Six months later, at another hospital, it was found that abnormal discharges could be precipitated by photic stimulation.

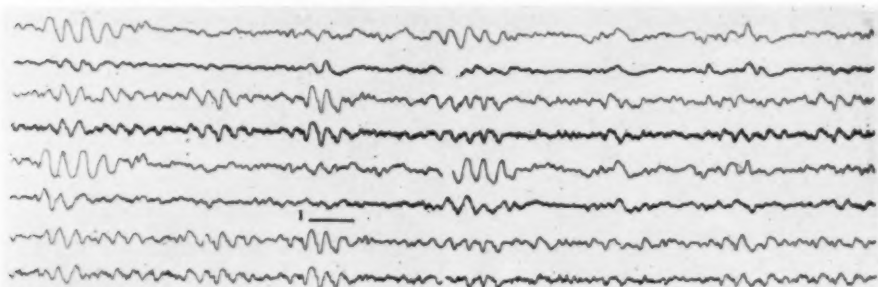
At that time he had increased ataxia and dysarthria and periodic involuntary jerking of his extremities. A few months later psychological testing revealed some intellectual deterioration.

He was placed on asparagine in combination with diphenylhydantoin and phenobarbital. He continued to have frequent myoclonic jerks, but it was felt by some examiners in 1956 that there was a "modest gain" in his emotional adjustment. Intellectual and neurological status were essentially unchanged.

A repeat electroencephalogram showed gross abnormalities, consisting at times of periodic slow-wave bursts recurring every four to six seconds.

Fig. 8.—Monopolar leads. Reference leads, both ear lobes, grounded.

1, right prefrontal; 2, right anterior temporal; 3, right parietal; 4, right occipital; 5, left prefrontal; 6, left anterior temporal; 7, left parietal; 8, left occipital.



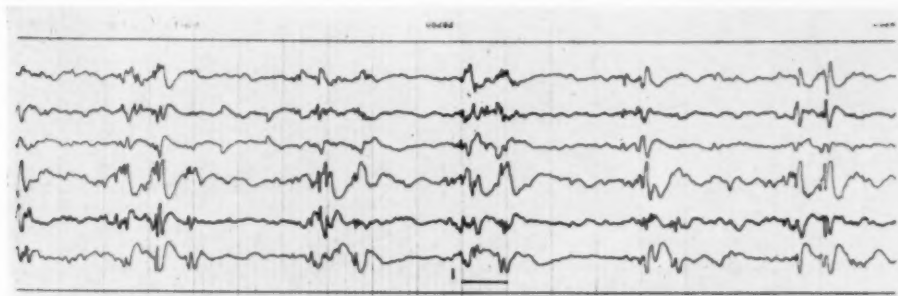


Fig. 9.—Same as Figure 6.

CASE 9.—The patient was first seen at the age of 11 months. He was born with multiple congenital defects. He did not feed spontaneously and required tube feedings for a number of weeks. He remained in another hospital during the first eight months of his life. When the infant was taken home by his parents, they noted that he was blind and apparently also deaf. They also noted periodic jerking movements of all extremities, the episodes lasting for a few months.

Examination on admission to the Neurological Institute showed that the child was microcephalic with marked asymmetry of the head, marked scoliosis of the spine, and bilateral equinovarus deformities. The child could not lift his head and appeared to be blind. There was marked, generalized spasticity, most pronounced in the lower limbs.

The cerebrospinal fluid contained 3 cells per cubic millimeter and a protein of 15 mg. per 100 cc. X-ray studies showed congenital malformation of the skull and premature incomplete synostosis of the sagittal suture with microcephaly. In addition, retarded maturation and moderately severe generalized rarefaction of bony structure were found.

The child slept most of the time. It was difficult to arouse him even for feeding. The myoclonic movements were fairly well controlled on diphenylhydantoin sodium 0.06 gm. a day and phenobarbital 0.015 gm. b. i. d. The diagnosis on discharge was cerebral maldevelopment of unknown etiology with microcephaly, spastic quadriplegia, convulsive disorder, and mental retardation.

The EEG record consisted of periodically recurring synchronous bursts of medium- to high-voltage 2-4 cps wave and spike-and-wave activity in all leads (Fig. 9). At times, only spikes were noted. There was a slight left preponderance of these bursts, which occurred at five- to six-second intervals. A repeat EEG in April, 1956, was identical with the earlier one.

He was readmitted at the age of 2½ years. His clinical status was essentially unchanged. He

had persistent spastic quadriplegia and more marked difficulty in swallowing. Myoclonic movements were again seen in all extremities, and there were at times continuous twitchings of the tongue and lips. Marked deformities of both hands were also noted. Laboratory findings were again unremarkable except for a hemoglobin of 8.6 gm. per 100 cc. and a red cell count of 2,980,000 per cubic millimeter.

CASE 10.—A 56-year-old right-handed woman was well and working until the end of May, 1954, when she began to complain of "constant buzzing in her ears." One week later she had obvious difficulty in comprehension and verbal expression. After two weeks, she was very restless, especially at night, and completely mute. Two days prior to her admission to the hospital she was noted to drop objects held in her right hand and to favor her right lower limb. About the same time intermittent jerking of her right shoulder appeared. Eight weeks after the onset of her difficulties she was admitted to the Neurological Institute.

On admission she presented a mild fever, mild tachycardia, and tachypnea. She was very restless, uncooperative, and out of contact with her surroundings and laughed inappropriately. Neurological examination revealed a constant coarse tremor and intermittent myoclonic jerking of the right upper and lower limbs. She walked with short, shuffling steps and with marked tendency to fall to either side. When standing, she fell in any direction whether the eyes were open or closed. Moderate cogwheel rigidity was present in all limbs, being most marked in the right upper extremity. There was no apparent weakness. All movements showed marked decomposition. Deep tendon reflexes were all hypoactive but equal on the two sides, and there were no abnormal reflexes. She responded vigorously to pain stimuli. Other sensory modalities could not be evaluated. There were occasional rolling, searching movements of the eyes, and facial twitching.

Laboratory studies, including repeated spinal fluid examinations, were normal. No virus could

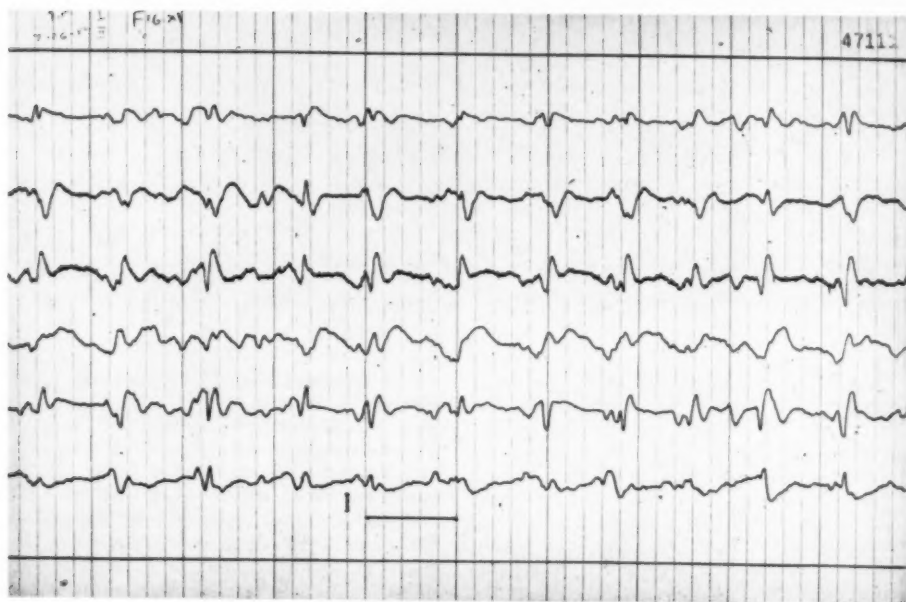


Fig. 10.—Bipolar leads.

1, right subfrontal-right prefrontal area; 2, right-left prefrontal areas; 3, left prefrontal-left subfrontal area; 4, right anterior temporal-right motor area; 5, right-left motor areas; 6, left motor-to left anterior temporal areas.

Calibration=50 μ v. Time=one second.

be isolated from several blood and spinal fluid specimens. X-ray studies of the chest showed generalized enlargement of the heart. Skull films were normal. A pneumoencephalogram revealed diffuse cerebral atrophy of moderate degree.

The electroencephalogram on the sixth hospital day showed a pattern of synchronous, fairly continuous bursts of irregular slow-wave and slow-spike activity in all leads. Figure 10 shows discharges at a rate of about 60 a minute. The pulse rate at the same time was about 90 a minute.

The patient appeared to become mentally more obtunded day by day. For a period of one week there appeared to be a mild right hemiparesis. One week after admission, choreiform movements and myoclonic jerks of the left upper and lower limbs were seen intermittently, particularly when she was disturbed. After 20 days of hospitalization, persistent myoclonic twitches of all limbs and of the head and neck were observed. The patient was semicomatose, responding only to deep pain stimuli. At times, athetoid movements could also be seen. Cogwheel rigidity became pronounced in all limbs. The temperature was always slightly elevated and rose occasionally to 102.5 F. Slight tachycardia was persistent. The abnormal movements increased, and the coma deepened. Thirty-

two days after admission the patient rapidly became cyanotic and died.

Necropsy.—Postmortem examination showed diffuse degeneration of the cerebral cortex, most marked in the frontal lobes. No etiological diagnosis was made. The lesions resembled those commonly seen as a result of diffuse vascular insufficiency. The vessels, however, showed no definite abnormality. Virus studies were negative.

CASE 11.—A 47-year-old right-handed housewife had a history of mild bifrontal headaches of many years' duration. Six months prior to admission she had "slight personality changes" and two months later complained of an increase in the severity of her headaches. About the same time she occasionally dropped objects held in her right hand. Two weeks prior to admission, her right upper limb became grossly ataxic, and she had difficulty in writing or cutting her food. She complained also of paresthesias in her right hand and forearm. Slurring of speech and intellectual deterioration became progressively more prominent during the last weeks prior to admission.

On admission the patient showed definite psychiatric abnormalities, consisting of impairment of recent memory, inability to concentrate, and difficulty with simple calculations, and she was quite euphoric. On neurological examination she was

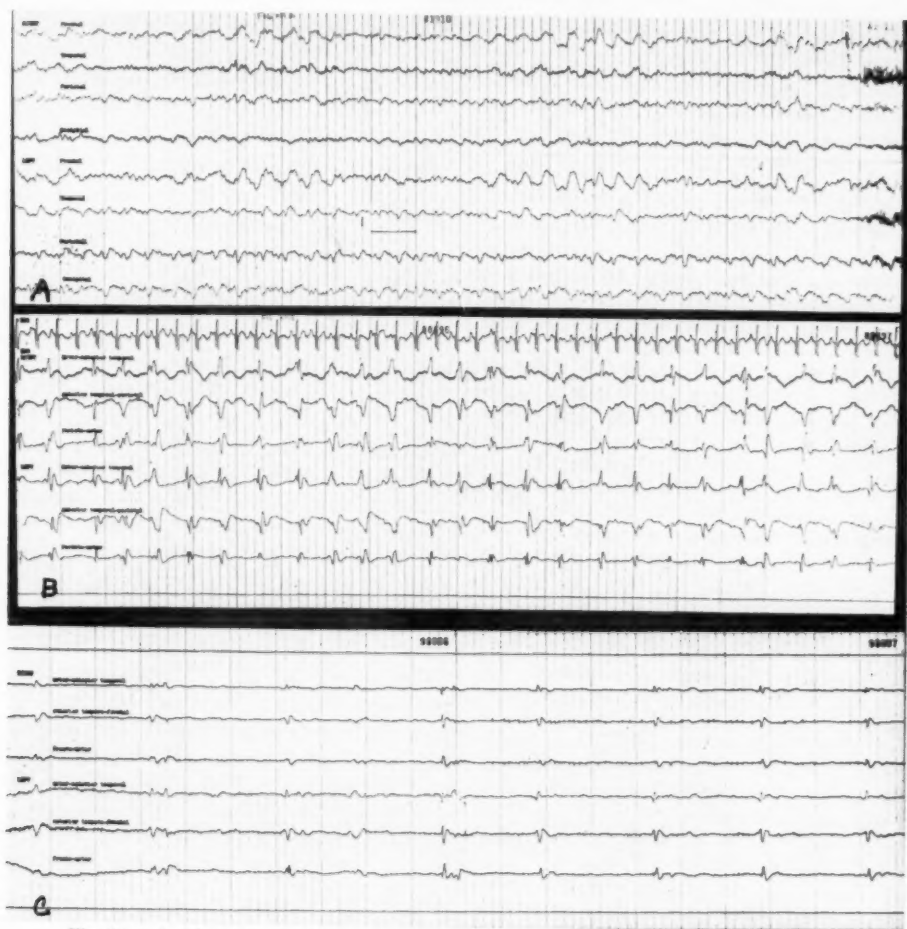


Fig. 11.—A: Monopolar leads, as in Figure 8.

B: Top: Electrocardiogram.

EEG: 1, right motor-right anterior temporal area; 2, right anterior temporal-right parietal area; 3, right parietal-right motor area; 4, left motor-left anterior temporal area; 5, left anterior temporal-left parietal area; 6, left parietal-left motor area.

C: Leads as in Figure 6.

found to be ataxic. There was decomposition of movement of both upper limbs, particularly the right. No gross motor or sensory deficits were noted. Speech was slurred; vertical nystagmus was present on upward gaze. Aside from an elevated sedimentation rate and evidence of severe bacterial cystitis, all laboratory studies were negative.

Psychological testing, performed on the fifth hospital day, revealed organic dysfunction with intellectual impairment and "scattering" of her performance.

Repeated electroencephalographic studies were performed. The first, on the day after admission,

showed a large slow-wave focus on the left side. During hyperventilation, bilateral bursts of high-voltage 2-3 cps wave activity were seen, especially in the frontal areas, recurring every eight seconds (Fig. 11A). This pattern changed gradually and about three weeks after admission slow spike and spike-and-wave discharges appeared at a rate of 70-75/min., at first a little higher on the left side and occasionally accompanied by myoclonic movements. Later on, the amplitudes became equal bilaterally. Eight weeks after admission, when she was in deep coma, the record showed the spike-and-wave discharge (75/min.) (Fig. 11B) almost continuously, associated with myoclonic jerking

The electrocardiogram (first line) indicates a heart rate of 132/min.

Four and one-half months later, shortly before her death, the record (Fig. 11C) showed basically depressed activity with periodic synchronous bursts of slow-spike activity, recurring every three to four seconds. At that time no myoclonic movements were seen.

Soon after admission the ataxia became more pronounced. A right facial palsy and astereognosis of the right hand were noted. All signs became progressively more marked. A ventriculogram and a left carotid arteriogram were normal. On the 13th day myoclonic jerks were noted over the right side of the body, particularly in the face. Consciousness became depressed, and the organic mental deficit became more marked. She had periods of precipitous crying and at times had visual and auditory hallucinations. One month after admission, the patient had almost continuous focal myoclonic twitching on the right and at times bilaterally. She became completely stuporous, responding only to painful stimuli. Five weeks after admission rigidity of all limbs was first noted, becoming progressively severer. The myoclonic jerks were more marked when the patient was disturbed. Extensor spasms of the upper limbs were noted after six weeks. A tracheotomy was performed because of inability to handle secretions. During the last two months of life she was in coma. Toward the end the myoclonic movements became less frequent and the dyskinesia ceased. The rigidity persisted. She ran a febrile course, at times septic in pattern, due to an intractable genitourinary infection. She died of cardiovascular collapse six months after admission.

Necropsy.—Necropsy revealed marked degeneration of the cerebellar cortex, in which the molecular and granular layers suffered much more severely than did the Purkinje cells. There were moderate degeneration of the corpus striatum and relatively mild degeneration of the spinal cord. The cerebral cortex was severely involved, with almost total disappearance of nerve cells throughout all portions. This degeneration was accompanied by an intense astrocytosis. No Alzheimer bodies, neurofibrillary changes, or senile plaques were seen. The blood vessels were well preserved. The anatomical diagnosis was "presenile degeneration of the central nervous system" (corticostriato-cerebellospinal degeneration). It was felt that this was a variant of the Jakob-Creutzfeldt syndrome.

Comment

Radermecker, first in 1949¹ and later in 1951,³ reported on the EEG findings in cases of subacute sclerosing leukoencepha-

litis (van Bogaert type⁶). He described the periodic appearance of high-amplitude slow-wave activity against a background of progressively altered basic rhythms. He thought that the movements seen in this disease were related to those seen in myoclonus epilepsy.

In 1950, Cobb and Hill² described the EEG findings in five cases of subacute progressive encephalitis, four of the Dawson type^{4,5} and one of the van Bogaert type. They, too, reported the progressive disappearance of normal activity and the emergence of periodic high-voltage slow waves, synchronous in all leads, repeating at intervals of approximately eight seconds. Involuntary movements seen in these cases occurred simultaneously with the slow-wave bursts. They considered the EEG changes characteristic.

Fanconi, Kramer, and Marthaler,⁷ reporting on seven cases of subacute encephalitis of both the Dawson and the van Bogaert variety, described similar EEG findings. They stated that the EEG findings were "pathognomonic of subacute encephalitis" and that they did not appear with central nervous system diseases of different etiology. Weingarten and Seitelberger⁸ reported on similar EEG records in cases of subacute sclerosing leukoencephalitis.

Pampiglione and Martin⁹ studied four patients who had electroencephalograms showing periodic synchronous bursts of slow, high-voltage activity. One patient was diagnosed as having lipid disease of the brain. Another had subacute sclerosing leukoencephalitis. In a third patient, a "psychopath without seizures," the periodic bursts appeared after prolonged photic stimulation. The fourth patient, who had grand and petit mal epilepsy, demonstrated periodic bursts after acoustic stimulation of varying duration while asleep, possibly related to "K complexes."

Watson and Denny-Brown,¹⁰ in a study of myoclonus epilepsy as a symptom of diffuse neuronal disease, described in detail three patients, two of whom were brothers. The two brothers died. In one, autopsy

showed diffuse central nervous system degeneration associated with amaurotic familial idiocy. All three had abnormal EEG findings, namely, synchronous and asynchronous bilateral bursts of slow-wave and spike-and-wave activity. The authors pointed to the variability in the clinical picture, even in the same patient at different times. In their opinion these electroencephalographic changes "are symptomatic of a whole class of disorders" characterized by severe diffuse degenerative encephalopathy.

Cobb, Martin, and Pampiglione¹¹ described the EEG findings in 12 children, all in the first decade of life, for whom the diagnosis of cerebral lipoidosis was made. The commonest EEG change consisted of recurrent high-voltage single sharp waves, usually in all leads and often bilaterally synchronous against a background of disorganized slow activity.

Jones and Nevins¹² described the clinical and postmortem findings in two patients, both in their 50's, who had features of myoclonus epilepsy. Electroencephalographic studies in both showed "generalized repetitive discharges often with spike components, the discharges remitting periodically either spontaneously or upon afferent stimulation." On autopsy both patients showed diffuse subcortical degeneration, which the authors ascribed to a "functional vascular impairment." They pointed out the similarity of their EEG findings to those seen in subacute encephalitis.

Radermecker,^{13,14} in two recent extensive reviews on the EEG in the encephalitides, reaffirmed his earlier impression that the periodic synchronous slow activity was seen only in cases of subacute leukoencephalitis with or without inclusion bodies. He reviewed 35 cases, 14 from his own series, which had been verified anatomically and in which EEG studies had been done. He pointed out that unless serial EEG's are performed the periodic synchronous bursts may be missed.

In the same studies he reviewed electroencephalographic findings reported in a

variety of other forms of encephalitis, including acute bacterial and viral meningitides with cerebral involvement. He reported on 10 cases of proved herpes simplex encephalitis, one from his own series, with no evidence of periodic synchronous bursts of slow-wave activity in any of them. His review also covers cases of encephalitis associated with infectious mononucleosis, measles, rubella, chickenpox, vaccinia, grip, poliomyelitis, rabies, dementia paralytica, and trypanosomiasis.

Most authors thus consider the periodic bursts in the EEG as specific for subacute leukoencephalitis, though Radermecker¹ himself noted that similar changes develop in some cases of myoclonus epilepsy.

A few authors, notably Watson and Denny-Brown,¹⁰ suggest the possibility that the EEG findings have a wider significance. This opinion would also find support in the observations of Pampiglione and Martin,⁹ who under special conditions found periodic bursts in response to prolonged photic or acoustic stimulation.

The original reports¹⁻³ lead to the impression that this EEG abnormality is found only in patients in the first two decades of life. Jones and Nevins,¹² on the other hand, saw it in patients in their 50's.

Our own experience strongly suggests that this EEG pattern is an indication of diffuse cerebral impairment, which may be transient or permanent, with structural changes of varying severity, not limited to any age group and of nonspecific etiology. In our cases we have seen it associated with certain clinical features, most of which were seen fairly constantly (Table). This group of symptoms, suggestive of a syndrome, consists of organic mental impairment, myoclonic seizures, generalized convulsions, rigidity, and dyskinesia of a choreoathetoid pattern. The organic mental impairment was present in all 11 cases but was transient in 3 of them. In several cases mental changes were seen early in the illness. They were the presenting symptom in three cases (1, 10 and 11). Consciousness was impaired

in all cases, at least for a time. Confusion, disorientation, impairment of memory, restlessness, and irritability were commonly noted. Three patients had visual hallucinations, and two had paranoid delusions. In three instances the mental changes were accentuated by high fever and cleared after the temperature had become normal.

All 11 patients had seizures. Eight had generalized convulsions, and nine had myoclonic seizures. In six both seizure manifestations were observed. They were transient phenomena in three.

Rigidity was seen in seven cases. It was absent in one case of encephalitis and in all three cases of Unverricht's myoclonus epilepsy. In the cases with fatal outcome, rigidity progressed to a picture of decerebration. Chorea-athetoid movements were seen in eight patients. They were absent in two of the patients with myoclonus epilepsy and in the patient with infectious mononucleosis.

Autopsies were performed in the four cases with fatal outcome (Cases 1, 2, 10, and 11). In all four instances extremely severe diffuse cortical involvement was found. All but Case 10, furthermore, showed widespread, though less severe, involvement of the subcortical white matter, basal ganglia, thalamus, and brain stem. The case of Jakob-Creutzfeldt disease showed severe degeneration of the cerebellar cortex and some changes in the spinal cord in addition. Some cerebellar degeneration was also found in the case of subacute inclusion body encephalitis (Case 1).

In Case 9 severe diffuse brain damage was diagnosed on the basis of severe cranial malformation with microcephaly and the clinical picture of quadriplegia.

Three patients recovered, two fully and one with persistent psychiatric deficit, classified as "behavior disorder." They had suffered, respectively, from encephalitis with infectious mononucleosis and encephalitides of unknown origin.

Three patients with Unverricht's myoclonus epilepsy have become progressively worse.

In view of the wide variety of etiologies in our group of cases, with recovery in a sizable group, we feel that it would be a serious mistake to make the diagnosis of subacute leucoencephalitis on the EEG pattern alone. This was done by several authors,¹⁶ whose patients recovered completely. While the diagnosis of subacute inclusion body encephalitis has been made in a single nonfatal case by biopsy,¹⁷ all other known proved cases have ended fatally.¹³

We have seen one additional case, not included in this study, in which periodic slow-wave bursts in the EEG were seen in a boy of 8 years who had postmeasles encephalitis. This child, 10 days after the clinical onset of measles, had an episode of unconsciousness with apnea and several hours later had a generalized convulsion in the hospital. The child, however, had none of the other features mentioned above and recovered completely. His EEG was fully normal on reexamination six weeks later.

In the cases with myoclonic seizures the periodic discharges in the EEG occurred synchronously with the fits. They were, however, recorded also when the fits were absent. Periodic EEG discharges were noted in the two cases who had no myoclonic seizures. In the first case (Case 1), the EEG discharges persisted during profound anesthesia when the movements were abolished.

Cases 10 and 11 present a variant in the electrical pattern. This consisted, at times, of a continuous discharge of slow spike-and-wave activity without depression of activity between. In Case 11, too, this was preceded, as well as followed, by regular periodic discharges. Thus the slow spike-and-wave discharge (Figs. 10 and 11) constitutes a link between the commoner paroxysmal patterns seen in the epilepsies and the periodic bursts.

We have reviewed about 20 cases of diffuse sclerosis and several of the infantile

form of Tay-Sachs disease. All had abnormal EEG patterns, but none showed periodicity. Nine additional cases of myoclonus epilepsy did not show periodicity in the resting records.

The periodic abnormalities in the electroencephalogram are seen in cases of verified severe lesions of the cortex with some additional involvement of subcortical structures. This strongly suggests that the discharges probably arise in deep subcortical areas, which, at least in the beginning, are still capable of some function. Release of still functional subcortical structures thus leads to the seizure phenomena and the EEG abnormalities. Involvement of basal ganglia, as in other diseases of these areas, leads to choreoathetoid dyskinesia and rigidity.

Transitory release of these structures may be the explanation for the clinical, as well as the electrical, phenomena in the milder cases with recovery.

Summary and Conclusions

Eleven patients were studied who had a distinctive abnormality in the electroencephalogram, namely, periodic bursts of synchronous slow-wave and spike-and-wave activity.

The case histories of these patients were analyzed. Four patients died, two of encephalitis and two of other forms of encephalopathy. One patient presented cerebral maldevelopment. Three patients suffered from Unverricht's myoclonus epilepsy. Three others had transient encephalitic processes of known or unknown etiology and recovered.

Thus the clinical pictures cover a wide range of severity, but all showed indications of cerebral impairment, transient or permanent, with features of an "organic" mental syndrome and other clinical manifestations, including myoclonic seizures and generalized convulsions, rigidity, and a dyskinesia of choreoathetoid pattern.

We suggest that the periodic synchronous discharges in the encephalogram are indicative of a certain level of cerebral, chiefly cortical, impairment.

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Lesse et al.

REFERENCES

1. Radermecker, J.: Aspects électroencéphalographiques dans trois cas d'encéphalite subaiguë, *Acta neurol. et psychiat. belg.* 49:222, 1949.
2. Cobb, W., and Hill, D.: Electroencephalogram in Subacute Progressive Encephalitis, *Brain* 73:392, 1950.
3. Radermecker, J., and Macken, J.: Aspects électroencéphalographiques et cliniques de la leucoencéphalite sclérosante subaiguë, *Rev. neurol.* 85:341, 1951.
4. Dawson, J. R., Jr.: Cellular Inclusions in Cerebral Lesions of Lethargic Encephalitis, *Am. J. Path.* 9:7, 1933.
5. Dawson, J. R., Jr.: Cellular Inclusions in Cerebral Lesions of Epidemic Encephalitis, *Arch. Neurol. & Psychiat.* 31:685, 1934.
6. van Bogaert, L.: Une leuco-encéphalite sclérosante subaiguë, *J. Neurol. Neurosurg. & Psychiat.* 8:101, 1945.
7. Fanconi, G.; Kramer, R., and Marthaler, F.: Clinical aspects of van Bogaert-Dawson's subacute encephalitis, *Schweiz. Arch. Neurol. u. Psychiat.* 72:379, 1953.
8. Weingarten, K., and Seitelberger, F.: Subacute Sclerosing Leukoencephalitis, *Wien. Ztschr. Nervenhe.* 6:65, 1952.
9. Pampiglione, G., and Martin, F.: Périodicité de quelques phénomènes cérébraux (étude électro-encéphalographique), *Schweiz. Arch. Neurol. u. Psychiat.* 71:277, 1953.
10. Watson, C. W., and Denny-Brown, D.: Myoclonus Epilepsy as a Symptom of a Diffuse Neuronal Disease, *A. M. A. Arch. Neurol. & Psychiat.* 70:151, 1953.
11. Cobb, W.; Martin, F., and Pampiglione, G.: Cerebral Lipidosis: An Electroencephalographic Study, *Brain* 75:343, 1952.
12. Jones, D. P., and Nevin, S.: Subacute Cortical Degeneration with Myoclonus and Epilepsy, *Tr. Am. Neurol. A.* 79:144, 1954.
13. Radermecker, J.: L'électroencéphalogramme dans les encéphalites et les déterminations cérébrales d'aspect encéphalitique, *Rev. neurol.* 93:369, 1955.
14. Radermecker, J.: Systématique et électro-encéphalographie des encéphalites et encéphalopathies, Paris, Masson & Cie, 1956; *Electroencephalog. & Clin. Neurophysiol., Supp.* 5, 1956.
15. Walsh, F. C.; Poser, C. M., and Carter, S.: Infectious Mononucleosis Encephalitis, *Pediatrics* 13:536, 1954.
16. Sanguineti, I., and Guareschi, A.: Contributo allo studio elettroencefalografico delle encefaliti, *Arch. psicol. neurol. e psichiat.* 13:549, 1952.
17. Kurtzke, J. F.: Inclusion Body Encephalitis: A Nonfatal Case, *Neurology* 6:371, 1956.

Experimental Study of Distant Effects of Acute Focal Brain Injury

A Study of Diaschisis

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Immediately following an acute transverse lesion of the spinal cord there ensues a state known as spinal shock.¹ Although not always recognized as such, an analogous situation can occur at more rostral levels, appearing, for example, subsequent to a rapidly developing lesion of a cerebral hemisphere. From clinical observations, von Monakow² formulated the concept that a transient depression of function can occur at a distance from a circumscribed lesion of the brain. He applied the term diaschisis to designate this circumstance.

It is pointed out by Riese³ that von Monakow's ideas have received little emphasis by English-writing neurologists. Riese suggests that this is because von Monakow's best-known publication, "Die Lokalisation im Grosshirn," appeared in Germany in 1914, at about the time of the outbreak of the First World War. He also emphasizes that this work has been little read in the United States, possibly because of the author's difficult style, which resulted from his Russian background. Nevertheless, there are clear statements of some of von Monakow's principles in certain English sources. "Blakiston's New Gould Medical Dictionary"⁴ defines diaschisis as

"an inhibition* of function in a region of the nervous system, due to a localized injury in another region with which it is connected by fiber tracts."

Riese,³ an obvious student of von Monakow, interprets diaschisis similarly. Although he feels that diaschisis and spinal shock as described by Sherrington¹ are not identical, it appears to the writer that the distinction has been too finely drawn. Sherrington wrote¹:

The whole of that depression or suppression of nervous functions which ensues forthwith upon a mechanical injury of some part of the nervous system and is of temporary nature may be conveniently included as "shock."

This surely suggests that the diaschisis of von Monakow is at least included in this "shock." Sherrington then goes on to discuss spinal shock as a particular case of the more general shock process.

The term "cerebral shock" appears in clinical use⁵ interchangeably with diaschisis to indicate the initial stage of flaccidity, areflexia, and altered consciousness which can arise immediately upon infarction of the brain. Although I have not traced the source of this phrase further, its intended analogy with "spinal shock" seems obvious enough. The term cerebral shock will be used in this communication rather than diaschisis because the lesions and their effects studied are cerebral and because spinal shock might also be considered an example of diaschisis.

*To avoid confusion with precedents of usage, the term inhibition is avoided in this communication. Instead, the change is designated simply as a depressive effect.

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Owing to the prevalence of infarction of the brain in man, cerebral shock is a far commoner event than spinal shock. Unlike spinal shock, however, the experimental method has not been previously directed to this problem. Despite von Monakow, this depression of activity is frequently explained today entirely on the basis of vascular rather than neuronal effects⁶; although distant vascular effects are not denied, it does seem that the von Monakow concept now receives little emphasis.

It seemed timely to put to test some questions related to cerebral shock. Would it be possible in the experimental animal to show depression of electrical activity of cerebral cortex remote from the site of an injury? If so, could a neuronal cause be distinguished from a vascular one? Such findings would support the neuronal basis for cerebral shock (diaschisis) as it was originally formulated from clinical observation.

Material and Method

All experiments were performed upon anesthetized cats. One cubic centimeter of 12% MgSO₄ (hydrated) and 12 mg. of pentobarbital sodium per kilogram were first given intraperitoneally. This was supplemented with a small amount of ether via tracheal cannula. An electrocorticogram (ECG) was recorded from the pial surface with bipolar or "monopolar" leads. With the latter a distant electrode common to all ECG channels was led from the midline periosteum overlying the posterior fossa. The head was held immobile in a head holder.

The optic radiation was stimulated⁷ with a pair of electrodes of fine steel wire insulated except at the tips and held firmly in place by an electrode carrier. This pair had an inter-electrode distance of 2 mm. and was inserted vertically through the suprasylvian gyrus at a point 9 to 10 mm. lateral to the midline and 12 to 15 mm. rostral to the posterior pole of the hemisphere to a depth of 9 to 10 mm. Single pulses of 0.1 msec. duration were delivered from a Grass stimulator. A transformer was interposed between stimulator and electrodes.

The electrical response of the optic cortex to single shocks in the radiation was led from the lateral gyrus with a distant lead on periosteum or from transcortical electrodes with an inter-

electrode distance of 2.5 mm., and was photographed from the screen of a cathode-ray oscilloscope.

Unilateral brain injury was produced by (1) electric cautery, (2) occlusion of one middle cerebral artery with a silver clip, (3) application of a piece of solid carbon dioxide to the cortical surface, and (4) removal of a block of cerebral cortex with a suction tip.

In some experiments the corpus callosum was divided in an aseptic operation several weeks in advance.

At the end of each experiment the position of the cathodal stimulating electrode was marked by electrolytic deposition of iron. This position was checked by an adaption of the Prussian blue-staining reaction.⁸

Results

In an earlier study,⁹ with pentobarbital anesthesia and using skull leads, no depressive effect upon the electroencephalogram contralateral to a lesion of one cerebral hemisphere was found. The combination of anesthetic agents employed in the present study resulted in a pattern of spontaneous activity more closely resembling that of the unanesthetized cat than does pentobarbital alone.¹⁰ In particular, the

TABLE 1.—Results of Various Methods of Brain Injury

Result	No. of Experiments
Electric cautery lesions	
Depressed amplitude of evoked response and ECG ipsilateral to lesion	4
Depressed amplitude of evoked response and ECG contralateral to lesion	1
Occlusion of middle cerebral artery	
Depressed amplitude of evoked response contralateral to lesion and ECG bilaterally	2
Depressed amplitude of evoked response contralateral and ECG amplitude ipsilateral but not contralateral	1
No effect on amplitude of evoked response contralateral or ECG bilaterally	1
Solid carbon dioxide lesions	
Depressed amplitude of evoked response contralateral and ECG bilaterally	3
Depressed amplitude of ECG bilaterally (evoked response not recorded)	1
Depressed amplitude of evoked response contralateral (ECG not recorded)	1
Depressed amplitude of ECG ipsilateral; no change of ECG or evoked response contralateral	1
No change of evoked response contralateral (ECG not recorded)	1
Limited cortical ablation	
Depressed amplitude of evoked response contralateral to lesion and ECG bilaterally	5
Depressed amplitude of ECG bilaterally (evoked response not recorded)	1
Depressed amplitude of ECG bilaterally; no effect on evoked response contralateral (smallest cortical ablation produced)	1

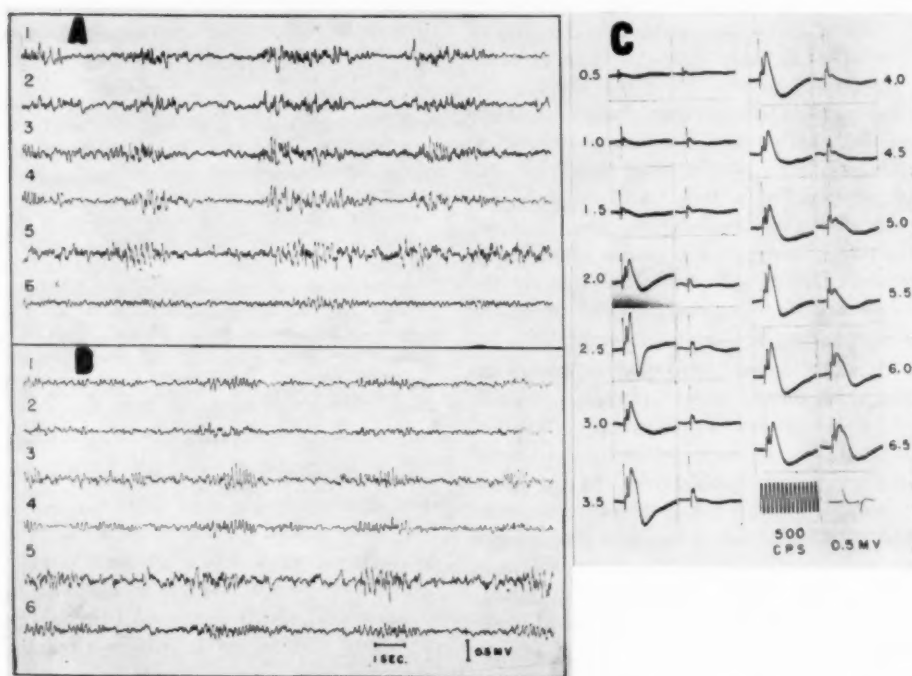


Fig. 1.—Multiple channels of ECG recording from left cerebral hemisphere and evoked response from left optic cortex before and after occlusion of right middle cerebral artery. ECG channel 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, left gyrus compositus; 3, posterior descending limb of left suprasylvian gyrus; 4, anterior position on left lateral gyrus; 5, left middle ectosylvian gyrus; 6, left anterior ectosylvian gyrus. A, control period before contralateral vascular occlusion; B, five minutes after vascular occlusion; C, evoked responses. First and third columns form a continuous series of responses to stimuli of increasing strength. Second and fourth columns are responses to same stimuli after the contralateral arterial occlusion. Upward deflection of base line in action-potential photographs indicates surface positivity. In this, and in the following Figures, numbers at side of action-potential records are actual stimulator voltage dial settings.

faster frequencies were more evident, although spindle bursts were also present. In addition to this selection of anesthetic agents, a more thorough search for a widespread depressive effect than that of the earlier study⁹ was undertaken by using direct leads from the pial surface. The electrical response of the optic cortex to single-shock stimulation of the optic radiation⁷ was also used in the analysis. Initially, in four cats, it was found that small cortical lesions produced by the electric cautery resulted in depression of ECG amplitude and evoked response in the same cerebral hemisphere. It was subsequently shown in one experiment that an electric cautery lesion

depressed the amplitude of the evoked response of the contralateral hemisphere and of the ECG on both sides. The results of these and subsequent experiments employing other methods of injury are summarized in Table 1.

The middle cerebral artery of one side was clipped during recording in four experiments. As a result of this injury, the evoked response was depressed in amplitude in the contralateral hemisphere in three of these experiments, and the ECG amplitude, in two (Table 1). One of these experiments is shown in Figure 1. There was a decline of ECG amplitude in the left cerebral hemisphere following occlusion of

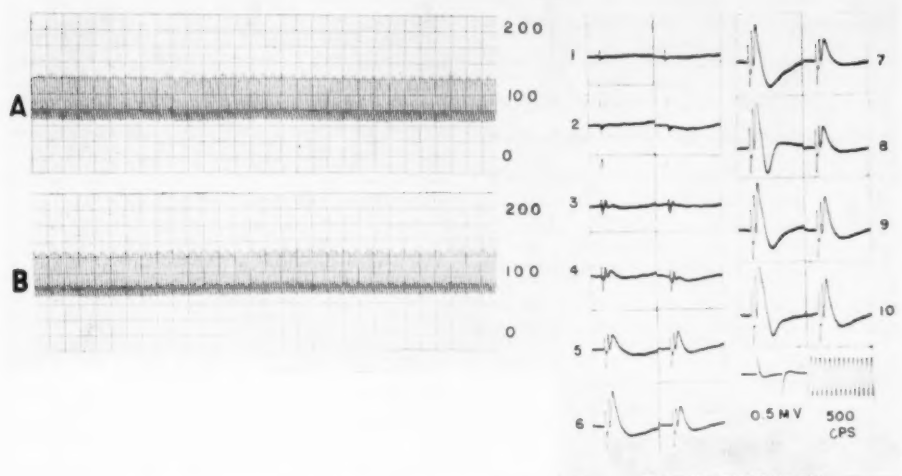


Fig. 2.—Evoked response of right optic cortex before and after occlusion of left middle cerebral artery. First and third columns form a continuous series of responses to stimuli of increasing strength. Second and fourth columns are responses to same stimuli after the contralateral arterial occlusion. *A* and *B* show femoral arterial blood pressure before and after the vascular occlusion, during the recorded series of action potentials. Numbers indicate pressure, millimeters of mercury.

the right middle cerebral artery. The faster frequencies were most affected, but there was also a decline of amplitude of spindle bursts. The electrical response of the optic cortex to single-shock stimulation of the radiation contralateral to the injury is shown in Figure 1C. This action-potential sequence developed more gradually in response to a series of shocks of stepwise increasing intensity after the injury than it did before. The early negative wave¹¹ was greatly diminished or abolished, and maximal amplitude response was now reached only at a higher stimulating voltage. The wave form was further modified in that the fourth cortical spike¹¹ was revealed more clearly by the disappearance of the early negative wave. Thus, the principal effects upon the evoked response were the production of a greater spread between threshold and maximal and the decrease or loss of the early negative wave.

Such changes suggested the possibility that occlusion of the middle cerebral artery caused a fall of systemic blood pressure, resulting in cerebral anoxia. That this ex-

planation did not hold true is shown by the observation (Fig. 2) that a similar change occurred unaccompanied by alteration of blood pressure. Maximal cortical response, including the main surface-positive component, did not attain the amplitude seen before the contralateral brain injury.

Unilateral brain lesions were made in seven cats with solid carbon dioxide (Table 1). An effect upon ECG and evoked response similar to that seen with vascular occlusion is shown in Figure 3, in which cortex of one hemisphere was injured by this method. There was a great decline of ECG amplitude on the side of the injury. In the structurally intact hemisphere there was some shift of ECG pattern, with a decrease in the amount of fast activity and a corresponding increase in the number of slow waves. Burst activity was little affected. ECG showed little recovery at the end of one hour. In Figure 3D a fast sweep of the oscillograph shows details of the early components of the evoked response, permitting an appraisal of the shock artifact, the optic radiation spike,¹² and the

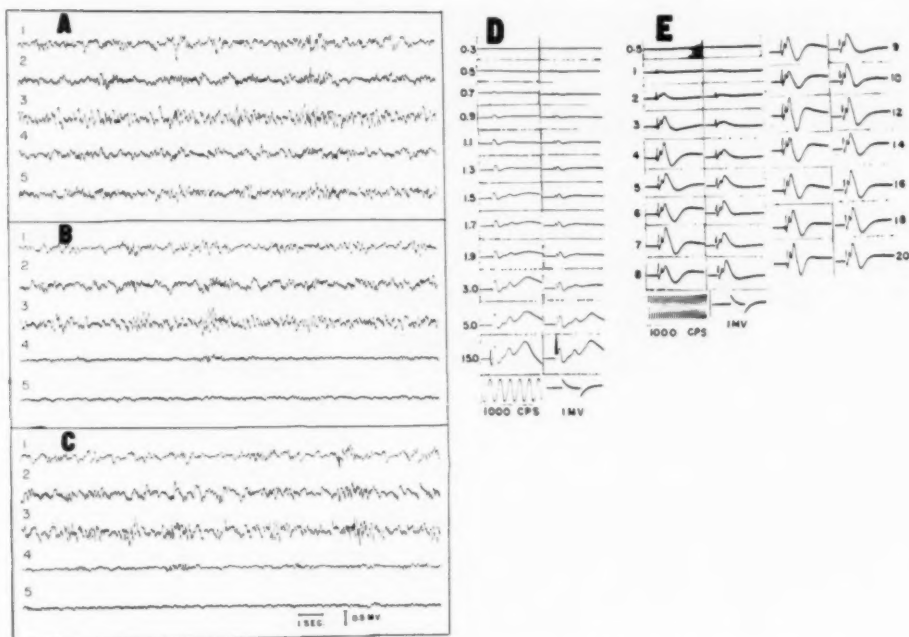


Fig. 3.—ECG, both cerebral hemispheres, and evoked response of left optic cortex, showing effect of large lesion (28×23 mm.) of right cerebral cortex produced by application of solid carbon dioxide. ECG channel 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, posterior descending limb of left suprasylvian gyrus; 3, anterior descending limb of left suprasylvian gyrus; 4, anterior position, right lateral gyrus; 5, right gyrus compositus. *A*, control period before right-sided injury. *B*, six minutes after the injury. *C*, 20 minutes after the injury. *D*, details of early part of evoked response shown on fast sweep. In first column (preinjury) initial small diphasic deflection is shock artifact. Next positive (upward) deflection is action potential of optic radiation. This is followed by the cortical fast spikes and the slower, underlying surface-positive deflection. Second column shows surface-positive shock artifact, slightly smaller optic radiation spike, and elevated threshold of cortical spikes after the injury. *E*, same evoked response, slower sweep. First and third columns form a continuous series of responses to stimuli of increasing strength. Second and fourth columns are responses to same stimuli after the contralateral injury.

first three cortical spikes.¹¹ The shock artifact changed from diphasic to surface-positive after the injury. Changes in the configuration of the shock artifact as a result of the injury posed a special problem, which is discussed in the following paragraphs.

In eight additional experiments the shock was balanced to produce a neat-looking shock artifact. This was done with a 2.5 megohm potentiometer across the stimulating pair, the center tap being connected to a third, remote electrode, usually in one temporal muscle. Although the least distortion of the initial part of the evoked response could be obtained by this method, it nevertheless proved unsatisfactory for the purpose of the study. Whenever this arrangement was used, a unilateral brain

lesion failed to affect the contralateral evoked response, although there might be a great reduction of amplitude of ECG contralateral to the lesion. The experiment was then performed, recording series of evoked responses, both with and without the potentiometer, before and after the injury. It was found that a depressive effect upon the evoked response contralateral to the side of injury was masked by use of the shock-balancing device and was plainly evident when the potentiometer was not used. Obviously, the combination of potentiometer and third electrode produced a different stimulus than did the bipolar arrangement alone. Furthermore, the shock could not be re-balanced to return it to its original configuration after the injury without changing the stimulus. The optic cortex response, thus evoked, was therefore an unsatisfactory indicator of the effect of a

distant brain injury. For these reasons, experiments performed thereafter, including all those listed in Tables 1 and 2, were conducted without such a shock-balancing method. Usually a remote electrode (paired with one on the lateral gyrus) was moved about on the periosteum in trial-and-error fashion until the least distortion of evoked response by shock artifact resulted. The two recording leads were therefore widely separated, except in a few experiments in which trans-cortical leads were used.

In many subsequent experiments unilateral brain injury was followed immediately by a change in the configuration of the shock artifact as recorded from the contralateral cerebral hemisphere. There were all conceivable types of change, a diphasic artifact becoming surface-negative, diphasic becoming surface-positive (Fig. 3), surface-positive becoming diphasic (Fig. 5), and surface-positive becoming surface-negative (Fig. 8). Also seen were diphasic shock artifacts in which both positive and negative components became smaller after the injury (Fig. 7), and a diphasic artifact in which both positive and negative components became larger after the injury. In other experiments there was no change of the shock artifact following the injury (Figs. 1, 2, and 4).

There are various possible explanations of these changes in the shock artifact. One of these would be that the manipulation of the brain required to produce the injury had shifted the position or otherwise altered conditions at the site of the stimulating electrode pair. However, changes in the shock artifact were seen equally well in those experiments in which there was a chronic section of the corpus callosum, although the cortical portion of the evoked response was unaffected (see text below and Table 2). For example, in Figure 7 both the positive and the negative components of a diphasic artifact became slightly smaller after the injury, and in Figure 8 the polarity was completely reversed without affecting the evoked response. Although it is possible that some changes in the shock artifact may have been due to changes at the site of the stimulating electrode, in view of the findings with chronic corpus-callosum section, it does not seem that the shock-artifact alterations were significant otherwise. An alternative explanation would be that the shock escape must pass through a wide extent of tissue on its way to the lead electrodes. The lesions, in altering the configuration of conductile tissue (ablation) or conductivity (death of tissue), might then alter the form of the shock artifact.

In Figure 3*D* the optic radiation spike is slightly smaller after the injury, although its threshold is not significantly changed. The cortical spikes had higher threshold

after the injury. Figure 3*E* illustrates the same response at a slower sweep. Again, the action-potential sequence developed more gradually to a series of shocks of increasing intensity, and maximal amplitude appeared at higher stimulating voltage after the injury than before. In this experiment, in contrast to that illustrated in Figure 1, the early negative wave reappeared at higher stimulus strengths, and wave form in general assumed the same configuration as before the injury. This was considered a less marked effect of contralateral brain injury than was a more enduring loss of the early negative wave.

Although there was frequently a decline in the amplitude of all components of the evoked response of the optic cortex, it has been noted that there was sometimes a selective decrease or loss of the early negative wave. This component was also found to be the one most likely to disappear with any accidental trauma near the site of recording. It has likewise been shown to be the component most susceptible to asphyxia.¹³ It therefore seems doubtful that there is anything specific about this change in relation to a remote cortical injury, as it is the component most frequently adversely affected by several types of noxae.

In these seven experiments in which the lesions were produced by solid carbon dioxide, there were four instances of amplitude depression of the evoked response and four in which ECG amplitude was decreased. Apparently, occlusion of one middle cerebral artery or cortical injury by application of solid carbon dioxide produced the contralateral effect upon ECG and evoked response only if the lesion was sufficiently large. It was considered desirable to find a method of focal injury which would have a more predictable effect. For this purpose, removal of cortex by suction (limited cortical ablation) proved most satisfactory. There were six experiments of this type, in which both ECG and evoked response were recorded (Table 1).

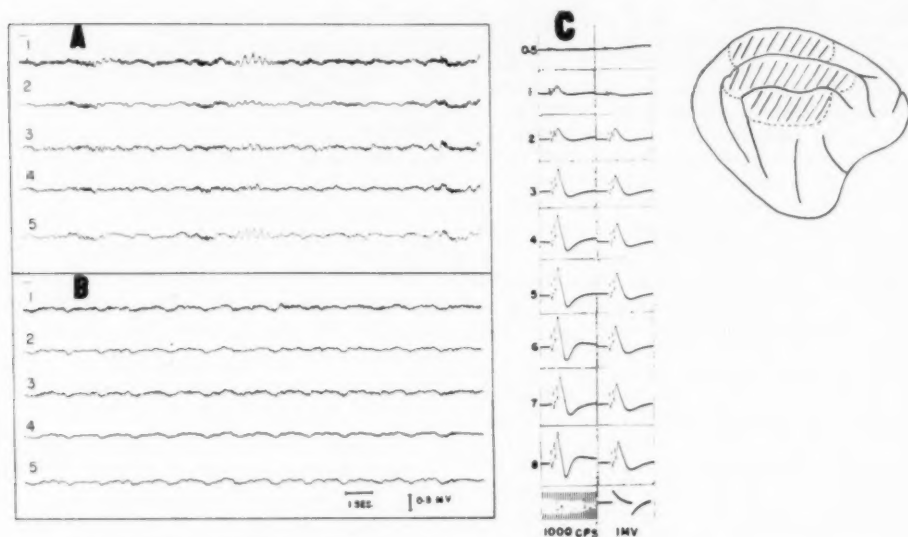


Fig. 4.—ECG, both hemispheres, and evoked response of left optic cortex, showing effect of removal of cortex on right. *A*, appearance of ECG before injury. 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, posterior descending limb of left suprasylvian gyrus; 3, anterior descending limb of left suprasylvian gyrus; 4, anterior position on right lateral gyrus; 5, right gyrus compositus. ECG changes following the injury are shown in *B*; pairs of evoked responses before and after the injury, in *C*. Size of cortical ablation is shown in accompanying diagram.

One of these is shown in Figure 4. There were a decrease in the amount of spontaneous fast activity and lowering of amplitude of spindle bursts in both cerebral hemispheres. In the evoked response, the radiation spike showed a consistent reduction of amplitude following the ablation. The decline of amplitude of the main surface-positive deflection and loss of the early negative wave were similar to those produced by other forms of injury. The size of the cortical lesion is of some interest for comparison with later experiments; it is shown in an accompanying diagram occupying portions of the lateral, suprasylvian, and superior ectosylvian gyri. This is the largest lesion of this group in which both ECG and evoked response were recorded. A similar, but less marked, reduction of amplitude of the optic radiation spike was also seen in Figure 3. Throughout this study, contrary to a preliminary report,¹⁴ there was a variety of changes of the radiation spike and its relation to the

succeeding cortical components. These are discussed in the following paragraphs.

In 17 of the 23 experiments listed in Table 1, the evoked response was recorded contralateral to the side of the lesion. In two of these the radiation spike was too distorted by the shock artifact for satisfactory measurement. Of the remaining 15, the radiation spike was unaffected by the injury in only 2. In six experiments the radiation spike was reduced in amplitude after the injury at all stimulating voltages (Figs. 2, 3, and 4). In five of these six the succeeding cortical components of the evoked response were also reduced in amplitude. In 3 of the 15 experiments the radiation spike was smaller after the injury at the lower stimulating voltages but larger than its preinjury size at its maximum. In each of these three experiments the succeeding cortical parts of the evoked response were smaller after the injury than before. In 2 of the 15 experiments the radiation spike was smaller after the injury at the lower stimulating voltages and equal in amplitude to its preinjury size at its maximum. In both of these, the cortical components were reduced following the injury. In the last 2 of these 15 experiments the radiation spike was larger at all stimulating voltages after the injury than before. In one of these two the cortical portion

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of the evoked response was reduced, but it was unchanged in the other.

There were also changes in the radiation spike contralateral to the side of an acute lesion in animals in which there was a chronic section of the corpus callosum (see below and Table 2). In none of these, however, was the amplitude of the succeeding, cortical portion of the response reduced in size. Of the eight experiments of this type listed in Table 2, the radiation spike was unchanged following the injury in only two. In one experiment the radiation spike was smaller following the injury, but only at the lower stimulating voltages. In another the threshold of the radiation spike was elevated following the injury, but the spike became of amplitude equal to that of the preinjury response as the voltage was increased. There was only one of the eight in which the radiation spike was smaller at all stimulating voltages after the injury. In the remaining three experiments the radiation spike was larger after the injury. In one of these, the succeeding, cortical portion of the response was also increased in size.

Obviously, most of the reductions of amplitude of the radiation spike (and the more marked reductions) occurred in those animals in which the corpus callosum was intact (e. g., Fig. 4). In some experiments in this study, while recording repeated responses to the same stimulus, it was found that there were spontaneous fluctuations of amplitude of the radiation spike, just as there were of the other components of the evoked response, although they were less marked in the case of the radiation spike. Such spontaneous fluctuations of the radiation spike, including variations of its maximal amplitude, are not uncommon with this combination of anesthetic agents. In this respect, it probably differs from pentobarbital alone, with which all other components of the evoked response show less variability. Doubtless some of the changes of the radiation spike recorded after the injury represent such spontaneous fluctuations. Changes of the radiation spike were not believed due to alterations of stimulating conditions, since, although there was equal possibility for such alterations in animals with chronic corpus callosum section, the changes of the radiation spike were less marked and the cortical portion of the response showed no decrease in the latter group. It seemed improbable that the difference in the effects of contralateral brain injury upon the optic radiation spike in the two groups, both with corpus callosum intact and with corpus callosum chronically sectioned, could be due to chance alone. In the absence of a more definite explanation, it may tentatively be suggested that the activity of radiation terminals is normally facilitated by transcallosal impulses. Loss of this facilitation might then account for this depression of the radiation spike

which sometimes follows the injury. It is apparent, however, that there are too many categories of change in the optic radiation spike to be all explained on the basis of a single cause. The net conclusion appears to be that, in the presence of a functioning corpus callosum, and immediately following a sufficiently large cortical injury, cortex of the contralateral hemisphere is less responsive to whatever volley reaches it via the radiation.

The smallest cortical ablation of these six experiments (without callosal section) measured 10×14 mm., and it had no effect upon the contralateral ECG and evoked response. Of these six ablations, only this one failed to bring about the depressive effect upon both ECG and evoked response in the opposite hemisphere. The next larger ablation measured 15×15 mm. (Fig. 5). This was the smallest ablation to be followed by the contralateral depressive change. Thus, when a sufficiently large area of cortex was removed, the depression of spontaneous and evoked activity in the contralateral hemisphere occurred in all (five out of five experiments). No attempt was made to recognize regional differences in the effect of cortical ablation; cerebral cortex was removed from the lateral and suprasylvian gyri and the superior portion of the ectosylvian cortex, including the visual cortex and/or cortex lateral to it.

The immediate contralateral effect of cortical ablation upon the ECG was sometimes marked. In Figure 6 a large area of cortex, measuring roughly 2×2 cm., was removed from the right lateral and suprasylvian gyri and the upper part of the auditory cortex. Before the injury (Fig. 6A) the ECG consisted principally of fast frequencies. A marked depression of fast activity on both sides was produced by the injury (Fig. 6B). There was a rapid return of fast waves only 25 minutes after the injury (Fig. 6C). Such a complete return of activity in so brief an interval was an exceptional finding; it indicated considerable variability of the crossed depressive effect.

It was considered possible that the contralateral depressive effect might be dependent upon the corpus callosum. To

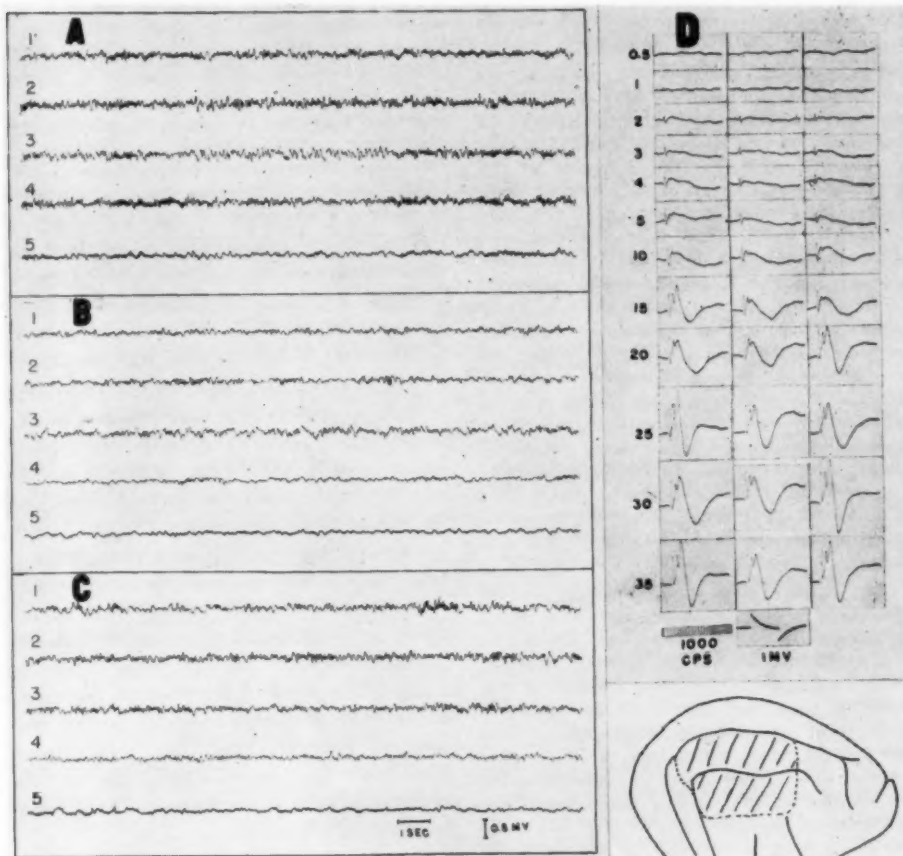


Fig. 5.—Smallest cortical lesion attempted which produced contralateral depressive effect. ECG channel 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, left anterior ectosylvian gyrus; 3, posterior descending limb of left suprasylvian gyrus; 4, anterior descending limb of right suprasylvian gyrus; 5, posterior descending limb of right suprasylvian gyrus. *A*, control period before injury. *B*, 10 minutes after injury. *C*, one hour after injury. *D*, evoked response of left optic cortex before and after injury. Third column shows complete recovery one hour after the injury. Cortical ablation on right as in accompanying diagram.

investigate this, the corpus callosum was divided during recording in four experiments (Table 2). Of these four experiments, there was bilateral depression of ECG in all and depression of evoked response on one side in both experiments in which it was recorded. Thus, the effect upon each cerebral hemisphere of sudden division of the corpus callosum was comparable to that of a limited unilateral cortical ablation upon the opposite hemisphere.

To investigate further the role of the corpus callosum, this commissure was sectioned some time in advance of the acute experiment in 17 cats. Owing to difficulties in exposure of the cortical surface resulting from the formation of adhesions between brain and overlying tissue, it was possible to elicit a satisfactory evoked response in only 8 of these 17 animals. In these 8, however, the ECG and evoked response recorded three or more weeks postopera-

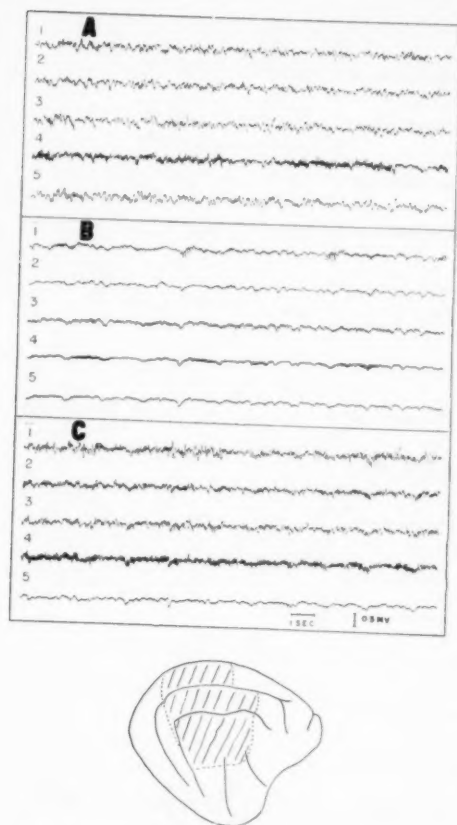


Fig. 6.—ECG, both sides, showing marked bilateral depressive effect of a large cortical destruction on right with rapid recovery on left. *A*, appearance of ECG before injury; 1, posterior position on left lateral gyrus; 2, left posterior ectosylvian gyrus; 3, left anterior ectosylvian gyrus; 4, anterior descending limb of right suprasylvian gyrus; 5, right gyrus compositus. ECG changes following the injury are shown in *B*. This is followed by return of activity, as shown in *C*, 25 minutes after the injury. Size of cortical lesion shown in accompanying diagram. Evoked response not recorded.

tively did not differ from those of cats not previously operated on. Of these eight cats, acute lesions were produced by solid carbon dioxide in one, by occlusion of one middle cerebral artery in two, and by a limited cortical ablation in five. The results are summarized in Table 2. Although there was no effect upon evoked response in any experiment and only a slight interhemispheric effect upon the ECG in one of

the experiments with the first two types of injury, the cortical ablations were more important for comparison with the earlier experiments, in which the corpus callosum was intact. In all five of these ablations, the area of cortex removed was larger than that of the smallest ablation to be followed by the contralateral depressive effect when the corpus callosum had been left intact (Fig. 5). In Figure 7 the corpus callosum had been sectioned six weeks earlier; a moderately large cortical ablation was made during recording. This lesion was intermediate in size between the smallest (Fig. 5) and the largest (Fig. 4) lesion of the earlier group. The ablation in Figure 7 had no effect upon the evoked response of the left optic cortex. A small amount of slow activity appeared in the ECG record on the left side after this injury on the right. The largest cortical ablation in this group is shown in Figure 8. This lesion is larger than the largest ablation in the group with corpus callosum intact (Fig. 4). The corpus callosum had been sectioned seven weeks earlier. Although the radiation spike was slightly smaller after the injury, the cortical portion of the response was unaf-

TABLE 2.—Results of Corpus Callosum Section

Result	No. of Experiments
Acute corpus callosum section	
Depressed amplitude of evoked response unilateral, ECG bilaterally	2
Depressed amplitude ECG bilaterally (evoked response not recorded)	2
Chronic corpus callosum section	
Occlusion of middle cerebral artery	
Depressed amplitude of ECG ipsilateral; no effect on ECG or evoked response contralateral	1
Depressed amplitude of ECG ipsilateral; slightly depressed ECG contralateral; no effect on evoked response contralateral	1
Solid carbon dioxide lesion	
Depressed amplitude of ECG ipsilateral; no effect on ECG or evoked response contralateral	1
Limited cortical ablation	
Depressed amplitude of ECG ipsilateral; no effect on ECG or evoked response contralateral	2
Depressed amplitude of ECG ipsilateral; increased slow activity contralateral; no effect on evoked response contralateral	1
Depressed amplitude of ECG ipsilateral; slightly depressed ECG contralateral; contralateral evoked response larger after lesion	1
Depressed amplitude of ECG ipsilateral; moderately depressed ECG contralateral; no effect on evoked response contralateral (Largest cortical ablation produced)	1

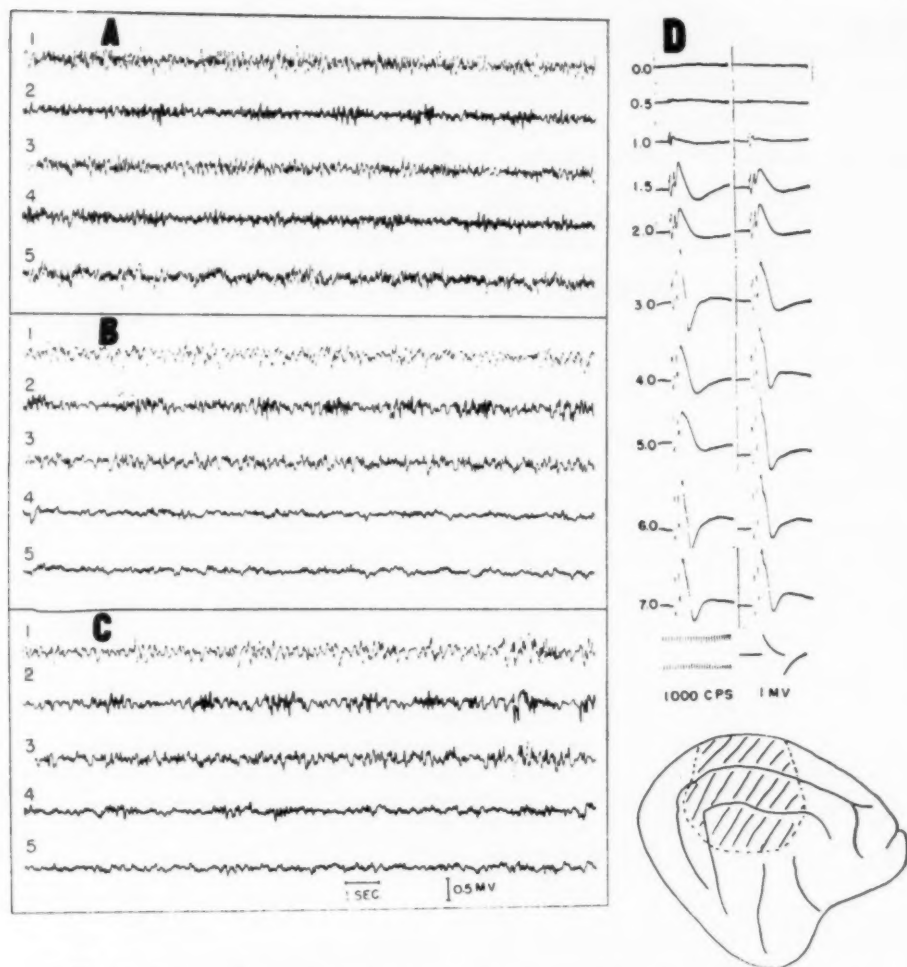


Fig. 7.—Corpus callosus sectioned six weeks in advance. ECG channel 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, left anterior ectosylvian gyrus; 3, posterior descending limb of left suprasylvian gyrus; 4, anterior descending limb of right suprasylvian gyrus; 5, posterior descending limb of right suprasylvian gyrus. *A*, control period before injury. *B*, six minutes after injury. *C*, 30 minutes after injury. Small amount of slow activity on left after injury on right. Little change one-half hour after injury. *D*, evoked response of left optic cortex before and after injury on right. Evoked response is not reduced in size after the injury (second column) when compared with control group, before injury (first column). Cortical ablation on right as in accompanying diagram.

ected. The ECG showed a distinct decline of amplitude on both left and right after this large lesion was made on the right side.

In summary, of these eight experiments with chronic corpus callosus section, none showed change of the evoked response fol-

lowing contralateral brain injury. There were depressive effects or slowing of the ECG on the side contralateral to the acute lesion in four of the eight. Three of these four were ablation experiments, and in them the severity of the contralateral effect was grossly correlated with the size of the

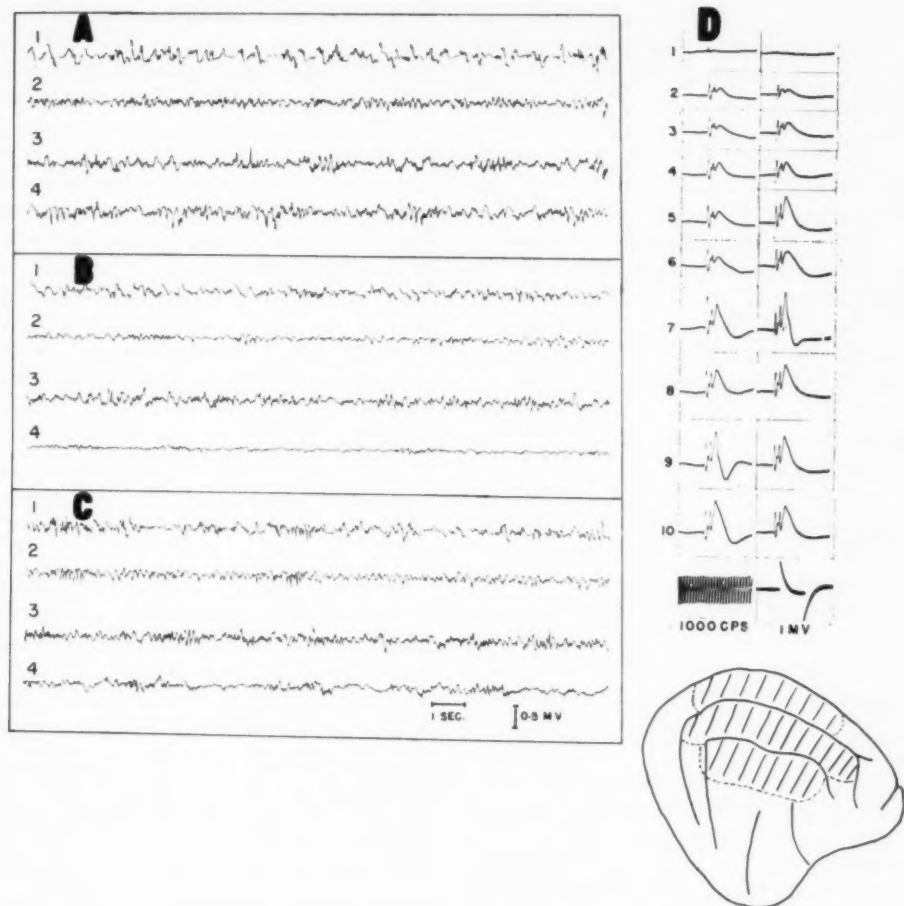


Fig. 8.—Corpus callosum sectioned seven weeks in advance. ECG channel 1, posterior position on left lateral gyrus (same electrode used for evoked response); 2, left posterior sigmoid gyrus; 3, left posterior ectosylvian gyrus; 4, right posterior ectosylvian gyrus. *A*, control period before injury. *B*, 10 minutes after injury. *C*, one hour after injury. Clearly depressed ECG activity following contralateral lesion; considerable recovery in one hour. Largest cortical lesion of this group, accompanying diagram. *D*, evoked response of left optic cortex before and after right-sided injury. Evoked response is not reduced in size by this large contralateral lesion.

lesion. However, these crossed ECG effects were, on the whole, less marked than those in the group with corpus callosum intact.

Comment

It was shown in this study that focal injury of cerebral cortex resulted in a transient depressive effect upon cortical electrical activity at a distance. A vascular cause for

this was largely excluded by using two regions having separate blood supply. There remained the unlikely possibility that this effect was due to widespread vasospasm. This, too, was eliminated when it was found that the depressive effect was dependent principally upon a neuronal pathway, the corpus callosum. It seems that essential criteria relating this depressive effect to diaschisis were fulfilled: The injury

was circumscribed; the depressive effect had a neuronal basis; it occurred at a distance from the injury; the fiber tract mainly responsible was identified, and the process was reversible. The depressive effect remote from the injury, as shown by the change in the spontaneous activity, was even more marked on the side of the injury than in the contralateral hemisphere. It seems reasonable to assume that at least one mechanism operative here was comparable to that which has been demonstrated for the contralateral effect and that, on the side of the injury, it must have been exerted through the various corticocortical connections originating and terminating within that hemisphere. The added factors of vasospasm, direct interference with blood supply, and direct trauma, however, could not be so readily controlled.

Although spinal shock is detectable only caudal to the transection, there is an inescapable similarity of the contralateral effect of the lesions in this study to what occurs immediately in the distal segment of a transected cord. For this reason, a comparison of the factors common to both spinal and cerebral shock now seems in order. Sherrington¹ found that, although spinal reflexes were temporarily depressed by transection of the cord, a later transection caudal to the first did not reproduce spinal shock. He concluded¹:

It seems to depend simply on solution of continuity of nervous channels, and this solution is practically equally great whether the actual trauma itself be relatively slight (a clean, sharply cut transection) or relatively severe (a contused and jagged transrapture), so long as in the two cases it involves an equal amount of the transverse area of the cord.

In the present study it has been found that interruption of the steady flow of impulses from their origin to their termination also forms the basis for diaschisis at the cerebral level.

A unified concept of the conditions necessary for the development of either spinal or cerebral shock may now be proposed. Impulses from one aggregate of neurons con-

stantly play upon the neurons of another, facilitating its activity. The first group is now destroyed; its function is suspended, or its fibers projecting to the second group are interrupted. The latter is thus deprived of one of its usual sources of facilitation. Consequently, it is less active during an interval immediately following the injury. There develops a wider expanse between its threshold and its maximal response to incoming stimuli, and its optimum preinjury performance may not be attainable. With time, the duration of which must depend upon the internal organization of the system and its other sources of afferent contributions, the second group of neurons assumes a greater autonomy than before the injury and ultimately functions at a level more closely approaching that present initially.

In considering this analogy with spinal shock, it might be argued that the electrical effects demonstrated are mild, in contrast with the severe clinical state of spinal shock. It must be admitted, however, that it would be unfair to attempt this correlation of a clinical state with an electrical effect (not to mention the difference of structural loci involved). It would be illogical to discount the cerebral shock interpretation of these experiments on the grounds that the effects noted here are quite brief as compared with the duration of the stage of cerebral shock in man. This disparity would be quite consistent with the observation that there are outstanding differences in the stage of spinal shock in different species, greater duration and severity being characteristic of higher position in the phylogenetic scale. It should also be mentioned that the longest duration of the depressive effect cannot be categorically stated because of limitations of the method. The effect has been observed undiminished for as long as one hour after the injury, but it is doubtful whether recording continued beyond that interval should be considered a reliable index of the functional state of the

anesthetized, exposed, and traumatized brain.

Although diaschisis has been defined as an "inhibition," this term is generally accepted to indicate an "active" inhibitory process. Evidence presented here indicates that this concept may now be reformulated: When injury suddenly suspends the activity of neurons directly, there is often (perhaps always) a secondary, untoward effect upon certain functionally related but structurally intact neurons as well. This effect is depressive in character and results from withdrawal of background facilitation.

There has been a fundamental reason for the production of circumscribed lesions in the investigation of cerebral injury. In the present study, and in an earlier work,⁹ the origin of the electrical change was ascertained in terms of the relation between two groups of synaptically related neurons (diaschisis) or among their constituent parts—axons, dendrites, and cell bodies (cerebral injury potential). In each of these studies the site of the injury was controlled, making possible this interpretation of the electrical change in terms of structure. This approach is to be contrasted with methods employing diffuse trauma for the study of cerebral electrical change. In the case of a mechanical force applied to the brain, with its attendant commotion of neurons, there is no way of knowing which neurons or which of their constituent parts are injured and which are not. Clearly, the structural alteration cannot be used to explain the electrical if both are changing simultaneously and if the spatial limits of the former are not definable.

It is suggested that the findings of this study represent a particular case of a general process, which also occurs with cerebral infarction and trauma in man. The interpretation of any experiment involving

acute brain trauma, either focal or diffuse, must entail some consideration of the role of diaschisis.

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REFERENCES

1. Sherrington, C. S.: *The Integrative Action of the Nervous System*, New York, C. Scribner's Sons, 1906.
2. von Monakow, C.: *Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde*, Weisbaden, J. F. Bergmann, 1914.
3. Riese, W.: *Principles of Neurology in the Light of History and Their Present Use*, New York, Nervous and Mental Disease Monographs, 1950.
4. Blakiston's New Gould Medical Dictionary, edited by H. W. Jones, N. L. Hoerr, and A. Osol, Philadelphia, The Blakiston Company, 1949.
5. Grinker, R. R., and Bucy, P. C.: *Neurology*, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949.
6. Cerebral Vascular Disease, Transactions of a Conference Held Under the Auspices of the American Heart Association, I. S. Wright, chairman; edited by E. H. Luckey, New York, Grune & Stratton, Inc., 1955.
7. Bishop, G. H., and Clare, M. H.: Responses of Cortex to Direct Electrical Stimuli Applied at Different Depths, *J. Neurophysiol.* 16:1-19, 1953.
8. Marshall, W. H.: An Application of the Frozen Sectioning Technic for Cutting Serial Sections Through the Brain, *Stain Technol.* 15: 133-138, 1940.
9. Kempinsky, W. H.: Steady Potential Gradients in Experimental Cerebral Vascular Occlusion, *Electroencephalog. & Clin. Neurophysiol.* 6:375-388, 1954.
10. Bishop, G. H.: Personal communication to the author.
11. Bishop, G. H., and Clare, M. H.: Sites of Origin of Electric Potentials in Striate Cortex, *J. Neurophysiol.* 15:201-220, 1952.
12. Bishop, G. H., and Clare, M. H.: Radiation Path from Geniculate to Optic Cortex in Cat, *J. Neurophysiol.* 14:497-505, 1951.
13. Noell, W. K., and Chinn, H. I.: Failure of the Visual Pathway During Anoxia, *Am. J. Physiol.* 161:573-590, 1950.
14. Kempinsky, W. H.: Spatially Remote Effects of Focal Brain Injury: Relation to Diaschisis, *Tr. Am. Neurol. A.* 81:79-82, 1956.

Relationship Between Anticoagulants and Hemorrhagic Cerebral Infarction in Experimental Animals

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Successful employment of anticoagulants in the treatment of thromboembolic disease outside the central nervous system is well documented and widely accepted. However, only in recent years has clinical support been given to utilization of these drugs when similar vascular lesions occur intracranially, and then only in selected cases in which damage is limited. Recently Siekert, Millikan, and Shick¹ listed only five currently accepted indications for use of anticoagulants in cerebrovascular disease.

Encouraging results from the use of anticoagulants in the treatment of the syndromes of intermittent insufficiency of the basilar and carotid arterial systems have been reported in detail by Millikan and Siekert.^{2,3} These authors subsequently described⁴ the administration of anticoagulants to patients who had received clinical diagnoses of thrombosis in the vertebral-basilar system. In their series, there was a mortality of 10%, as compared with a mortality of 43% in a similar group of patients not treated with anticoagulant drugs. Wright and McDevitt⁵ and Askey and Cherry⁶ demonstrated definite reduction in the incidence of the cerebral thromboembolic complica-

tions of heart disease through the long-term prophylactic employment of anticoagulants.

Whether anticoagulants should be used in treatment of cerebral thrombosis and infarction is not known. Luckey⁷ advocated such treatment in the belief that these drugs would increase the rapidity of recanalization, prevent future formation of cerebral thrombi, and reduce the number of complicating extracerebral thromboembolic episodes. In actual clinical employment of the drugs, however, hemorrhagic complications have been encountered. Stürup and Fog⁸ treated with anticoagulants 43 patients with cerebral apoplexy who had clear, colorless cerebrospinal fluid. These investigators were unable to draw definite conclusions concerning clinical improvement. They reported hemorrhagic cerebral complications in three fatal cases and concluded that to begin treatment with anticoagulants in the first 24 hours after the insult increased the risk. In treating six patients who had cerebral thrombosis, Duff⁹ was forced to abandon use of heparin and bishydroxycoumarin U. S. P. (Dicumarol) in two cases because of clinical deterioration. MacMillan and Brown¹⁰ noted hemorrhagic cerebral infarcts in three fatal cases of 489 cases in which extracranial thromboembolic disorders were being treated with anticoagulants. These hemorrhagic infarcts were considered further ground for considering use of anticoagulants to be contraindicated when recent "cerebral softening" is suspected.

Fisher and Adams¹¹ and Hicks and Black¹² demonstrated a high percentage of hemorrhagic infarcts in cases of cerebral infarction in which anticoagulants were not

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given. However, Blumgart and associates¹³ have demonstrated that use of anticoagulants did not increase the amount of hemorrhage in experimentally induced myocardial infarcts. Moyes and associates¹⁴ have shown that cerebral infarcts experimentally produced in dogs are more hemorrhagic if values for prothrombin activity are excessively low than in a control series in which prothrombin activity is normal.

Purpose

In view of all clinical reports, two basic problems challenge the general utilization of anticoagulants in treatment of patients who have had strokes. The first is the difficulty sometimes encountered in clinically differentiating cerebral hemorrhage from thrombosis or embolism. The second problem is directly concerned with what happens to a cerebral infarct in the presence of prothrombin activity reduced to a therapeutic level. It was with this latter problem in mind that we undertook to determine whether cerebral infarcts experimentally produced in dogs with prothrombin activity reduced to from 10% to 30% of normal would be more hemorrhagic than cerebral infarcts similarly produced in control dogs with normal prothrombin times.

Material

All dogs originally used in this investigation were in normal condition and weighed from 9 to 14 kg. Of these, 39 proved fit for retention in the experiment.

Brief anticipatory amplification will help in understanding of the material. In all 39 dogs, cerebral infarcts were experimentally produced. In 25 of the 39, reduced prothrombin activity also was experimentally produced (anticoagulant series). To 14 of the 39 animals, anticoagulants were not given (control series). To be considered "fit for retention in the experiment," a dog must show signs to indicate that cerebral infarction had actually developed; also, for at least 48 hours, he must have survived the surgical procedure and simultaneous injection necessary to production of the infarct. Although administration of the anticoagulant, in the anticoagulant series, might not begin until as much as seven and one-half hours after the operative

procedure, we believed that our requirement of 48 hours of survival after operation would give ample time for the anticoagulant to have effected satisfactorily reduced prothrombin activity.

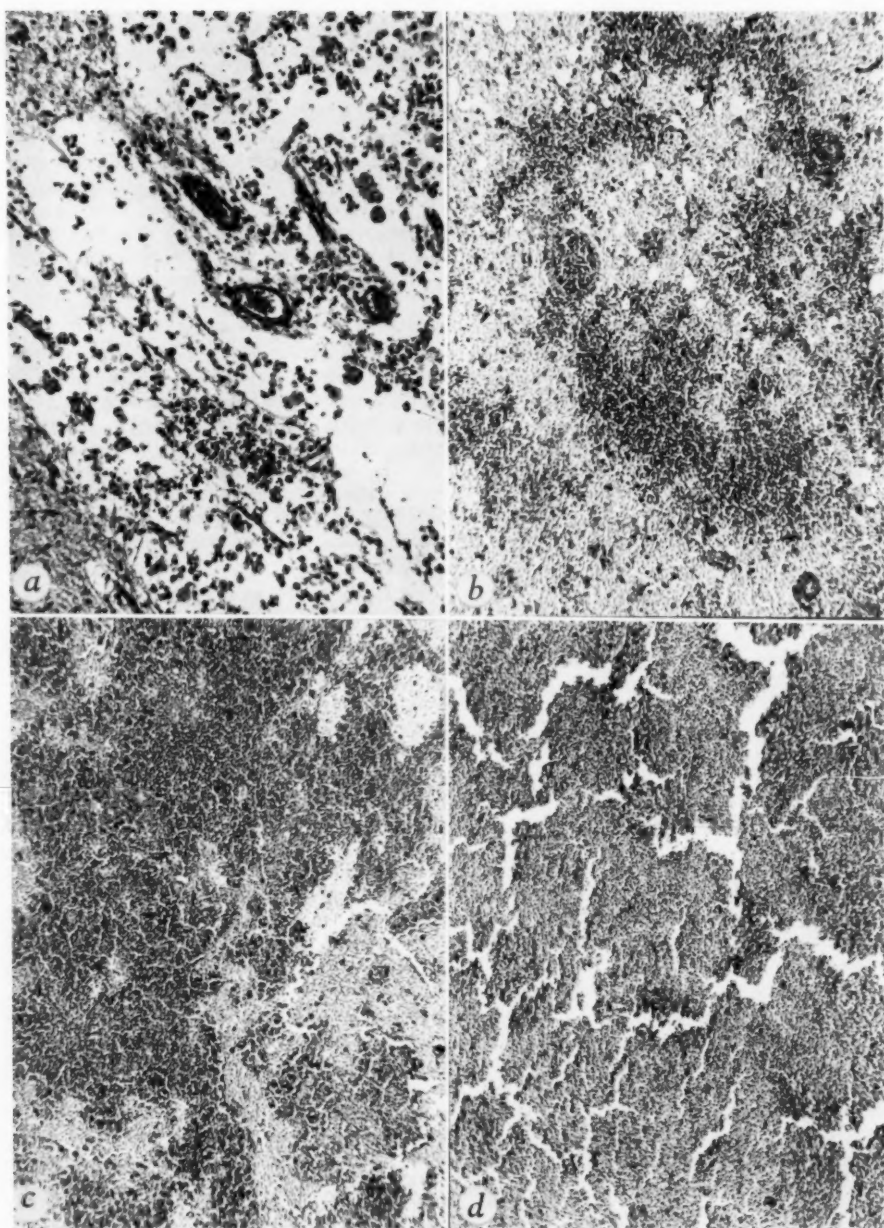
Method

Before the operation for production of the cerebral infarcts, control prothrombin times were established. The infarcts were produced by injecting 0.25 cc. of vinyl acetate into the right internal carotid artery of each dog, according to the standardized technique of Whisnant and associates.¹⁵ The surgical procedures were carried out between 8 and 10 a. m., all injections being performed by the same investigator.

The dogs were observed very carefully throughout the period of study. In the presence of a cerebral infarct, the animals would circle to the right, that is, toward the side of the lesion, and would present hemiparesis of the opposite side, involving one or both limbs. An attempt was made to evaluate the visual field defects of the dogs that had infarcts; however, the results were so variable and inconsistent that this examination was abandoned.

As has been said, control prothrombin times had been established before the injections of vinyl acetate. Determinations of prothrombin time were made by the modified Quick method described by Hurn, Barker, and Magath,¹⁶ in which dried rabbit brain is used for thromboplastin. A fresh batch of thromboplastin was prepared each week and a prothrombin activity curve constructed; 0.85% sodium chloride solution was used to dilute normal dog plasma to the required concentration. After preparation, each lot of thromboplastin was divided into six portions and was placed in the freezing compartment of a refrigerator. Each day, one tube was removed for use.

The anticoagulants used were ethyl biscoumacetate (Tromexan Ethyl Acetate) and bishydroxycoumarin. Initial total doses of 40 to 50 mg. of ethyl biscoumacetate and 8 to 10 mg. of bishydroxycoumarin were given to each dog of the anticoagulant series at 3:30 p. m. on the day of operation. Blood for determination of prothrombin time was withdrawn between 10:30 and 11:30 a. m. on all subsequent days until the prothrombin times became stabilized within the desired range. Thereafter, determinations were not made on Sundays. The desired range was that which produced prothrombin activity of 10% to 30% of normal (or prothrombin time approximately 2 to 2.5 times its control value). Usually values for prothrombin time had reached therapeutic range within 24 hours after the initial dose of anticoagulants had been given on the day of operation. Thereafter, the reduced prothrombin activity was maintained by



(a) Congestion of blood vessels with a few red blood cells outside the capillaries, Grade 1. (b) Extravasation of blood without distortion of involved tissues, Grade 2. (c) Extravasation of blood with distortion of involved tissues, Grade 3. (d) Extensive, confluent hemorrhage, Grade 4. $\times 100$.

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use of bishydroxycoumarin only. More of this anticoagulant was not needed until the third or fourth postoperative day. Whenever needed, it was given in sufficient dosage to hold the prothrombin times within the therapeutic range.

Whenever any of the 39 dogs died more than 48 hours, but less than 12 days, after the surgical procedure, the neck and cranial contents were carefully examined and the brain preserved in formalin, as will appear presently. All others of the 39 dogs were anesthetized by intravenous injection of pentobarbital sodium and were killed on the 12th postoperative day; they were similarly examined, and their brains were similarly preserved. Whenever the brain of a dog of one series was examined, the brain of a dog of the other series (one of approximately the same duration of life after the surgical procedure) was examined for comparison.

All the brains were fixed by keeping them immersed in a 10% solution of formalin for a minimum of two weeks. Thereafter the same person did all of the sectioning and another all the recording, now to be described: One cut each brain into seven standard coronal sections of nearly equal thickness. The other recorded the infarcts (both hemorrhagic and nonhemorrhagic) and the distribution of vinyl acetate on standard printed

forms corresponding with the seven coronal sections.

The quantitative method of Hill and associates¹⁷ then was employed to measure each infarct and its hemorrhagic component. In this manner the number of square millimeters of infarct that were hemorrhagic and the number of square millimeters of infarct that were nonhemorrhagic, at the surface of each of all seven sections of each brain, were determined. From these quantities the percentage of the area of each infarct that was hemorrhagic was calculated.

In the course of the procedures just described, representative sections from all infarcts had been made for microscopic examination. The sections had been taken from hemorrhagic portions if there were any such portions. If an infarct had seemed nonhemorrhagic on gross examination, the sections had been made from the most necrotic portion. The sections had been stained with hematoxylin and eosin. Material from animals of the control series, and of the anticoagulant series, had been treated in the same manner.

The slides now were taken at random for microscopic grading of the amount of hemorrhage that had taken place. The examiner did not know whether a given slide represented an animal of the control or of the anticoagulant series, nor did

TABLE 1.—Gross and Microscopic Findings

Dog	Survival, Days (Age of Infarct)	Hemorrhagic Portion of Infarct, Sq. Mm.	Nonhemorrhagic Portion of Infarct, Sq. Mm.	Total Infarct, Sq. Mm.	Percentage of Infarct Hemorrhagic	Microscopic Grade of Hemorrhage
Anticoagulant Series						
1	12	138	319	457	30.2	2
2	12	0	422	422	0	2
3	6	824	718	1542	53.4	4
4	12	180	77	257	70.0	3
5	3	449	1203	1652	27.2	4
6	6	760	786	1546	49.2	4
7	4	328	515	843	38.9	4
8	2	385	785	1170	32.9	3
9	5	451	648	1099	41.0	4
10	12	8	6	14	57.1	2
11	12	18	544	562	3.2	2
12	12	4	240	244	1.6	1
13	4	870	897	1767	49.2	4
14	12	165	947	1112	14.8	3
15	2	164	1527	1691	9.7	3
16	12	11	44	55	20.0	2
17	2	26	826	852	3.0	3
18	12	26	484	510	5.1	2
19	12	0	349	349	0	2
20	2	3	683	686	0.4	1
21	3	194	556	750	25.9	3
22	12	61	171	232	26.3	1
23	12	17	440	457	3.7	3
24	3	192	746	938	20.5	3
25	2	25	667	692	3.6	2
Control Series (14 Dogs)						
26	2	0	960	960	0.0	2
27	12	50	2060	2110	2.4	3
28	12	86	208	294	29.3	2
29	12	51	626	677	7.5	2
30	12	0	563	563	0	1
31	2	120	1085	1205	9.9	3
32	2	154	1379	1533	10.0	3
33	12	0	572	572	0	1
34	12	49	1006	1055	4.6	2
35	12	33	898	931	3.5	3
36	12	0	619	619	0	1
37	12	376	1232	1608	23.4	3
38	12	690	0	690	100.0	3
39	2	0	2248	2248	0	1

TABLE 2.—Percentages of Infarcts That Were Hemorrhagic on Gross Examination—Grouped Frequencies, from Table 1

Percentages	Number of Dogs	
	Anticoagulant Series	Control Series
0-9.....	10	10
10-19.....	1	1
20-29.....	5	2
30-39.....	3	
40-49.....	3	
50-59.....	2	
60-69.....		
70-79.....	1	
80-89.....		
90-100.....		1
Total.....	25	14

he know the gross findings relative to the brain from which the microscopic preparation had been made.

Under low-power ($\times 100$) magnification the field presenting the most hemorrhage was brought into view, and the following arbitrary classification was utilized:

Grade 1: Congestion of blood vessels with or without a few red cells outside the capillaries (Figure, a)

Grade 2: Extravasation of blood from the vessels without distortion of involved tissues (Figure, b)

Grade 3: Extravasation of blood from the vessels with distortion of involved tissues (Figure, c)

Grade 4: Extensive, confluent hemorrhage (Figure, d)

Results

In Table 1 are recorded gross and microscopic findings. That two of the dogs of the anticoagulant group had no gross hemorrhage and that one dog of the control series had an infarct which was entirely hemorrhagic are noteworthy.

In Table 2 the percentages given in Column 6 of Table 1 appear as grouped frequencies. The spread of cases is represented for each 10% increment of hemorrhagic infarct up to 100%. In each of nine instances of the anticoagulant series, 30% or more of the infarct was hemorrhagic; in only one instance of the control series was so much of the infarct hemorrhagic. In the anticoagulant series, then, hemorrhage tended to occupy a larger part of the infarct than in the control group.

The numbers of dogs representing each microscopic grade of hemorrhage in the infarcts are recorded in Table 3. If, in a given dog, several grades of hemorrhage were represented, we took for record the hemorrhage of maximal grade. Six infarcts of the anticoagulant series were of Grade 4. In the control group none of the infarcts were of Grade 4. Microscopic data, therefore, seem to justify the statement that infarcts of the dogs that received anticoagulants were characterized by more severely hemorrhagic components than were those of the control series.

In an attempt to determine what bearing age of the infarct had on severity of hemorrhage, as measured by microscopic grading, Table 4 was compiled. The number of days that a dog lived after the operation for production of the infarct was considered to be equivalent to the age of the infarct.

In the anticoagulant series, all of the dogs whose hemorrhages were graded 4 died in four to seven days. Of the 13 animals whose hemorrhages were graded 3 or 4, 11 died early; only 2 animals with hemorrhages of Grade 3 survived into the 12th day. On the other hand, 10 of the 12 dogs whose hemorrhages were of Grade 1 or Grade 2 survived into the 12th day. From this it can be assumed that, in the anticoagulant series, the severer hemorrhages were the less compatible with life.

In the control series hemorrhages of Grade 4 did not occur. The animals of this series either died shortly after the 48 hours following operation had elapsed or survived into the 12th day. Four of six dogs whose infarcts were graded 3 from the standpoint of hemorrhage lived into the 12th day after

TABLE 3.—Results of Microscopic Grading

Grade	Number of Dogs	
	Anticoagulant Series	Control Series
1.....	4	4
2.....	8	4
3.....	7	6
4.....	6	0
Total.....	25	14

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TABLE 4.—Grade of Hemorrhage and Age of Infarct

Series and Grade	Age of Infarct, Days * More Than										
	2	3	4	5	6	7	8	9	10	11 †	
Animals											
Anticoagulant											
1		1								3	
2		1								7	
3		3	2							2	
4			1	2	1	2					
Control											
1		1								3	
2		1								3	
3		2								4	
4											

* Equivalent to survival of animal after injection of vinyl acetate.

† Not more than 12 days.

operation, whereas six of eight dogs whose hemorrhages were of Grade 1 or Grade 2 survived into the 12th postoperative day.

It is evident in Table 4 that, after the initial impact of the cerebral infarction, no dogs of the control series died early, whereas eight dogs of the anticoagulant series that survived the initial effects did die early.

Comment

The findings of this study suggest that infarcts which developed among dogs that received anticoagulants were more extensively hemorrhagic than those which developed among control dogs. Infarcts of the majority of the control dogs were nonhemorrhagic (less than 20% of area), but the infarcts of just more than half of the anticoagulant group were hemorrhagic (greater than 20% of area). However, great variability in the amount of hemorrhage existed, and extremes were present in both groups. In the anticoagulant series were two dogs with completely nonhemorrhagic infarcts, and in the control group was one dog whose infarct was 100% hemorrhagic.

Since each infarct was graded microscopically and grossly, the question arises whether there is any correlation between these two methods. On gross inspection, hemorrhages of Grade 4 appeared to involve portions of the infarcts ranging from approximately 25% to 55%, while the hemorrhage of the infarct which on gross

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inspection appeared to be 100% hemorrhagic was graded only 3 on microscopic examination. It appears, therefore, that absolute correlation of the two methods of grading does not exist.

It should be emphasized that all of these findings apply to dogs with cerebral infarction in one hemisphere and should not necessarily be applied to other types of cerebrovascular disease.

Summary

Of dogs into whose internal carotid arteries vinyl acetate had been injected to produce unilateral experimental cerebral infarction, 39 met the two conditions for their retention in the investigation: The infarct developed, and the dogs survived the injection more than 48 hours. Twenty-five of these animals were given anticoagulants five and one-half to seven and one-half hours after injection of the vinyl acetate, and their prothrombin activities were maintained at 10% to 30% of normal during their subsequent course. The remaining 14 dogs were not given anticoagulants and were used as controls.

Gross quantitative measurement of the infarcts was made, and the amount of hemorrhage that had taken place was graded microscopically. The results of this experiment indicate that cerebral infarcts were more hemorrhagic when dogs were given anticoagulants soon after infarction had been induced than when the dogs did not receive anticoagulants; also, that after the initial impact of the infarction had passed, the mortality rate among dogs that thus had received anticoagulants was significantly higher than it was among the animals to which anticoagulants had not been given.

Section of Neurologic Surgery, Mayo Clinic.

REFERENCES

1. Siekert, R. G.; Millikan, C. H., and Shick, R. M.: Current Indications for the Use of Anticoagulant Drugs in Cerebrovascular Disease, *Circulation* 13:725-728 (May) 1956.
2. Millikan, C. H., and Siekert, R. G.: Studies in Cerebrovascular Disease: I. The Syndrome of

- Intermittent Insufficiency of the Basilar Arterial System, *Proc. Staff Meet. Mayo Clin.* 30:61-68 (Feb. 23) 1955.
3. Millikan, C. H., and Siekert, R. G.: Studies in Cerebrovascular Disease: IV. The Syndrome of Intermittent Insufficiency of the Carotid Arterial System, *Proc. Staff Meet. Mayo Clin.* 30:186-191 (May 4) 1955.
4. Millikan, C. H.; Siekert, R. G., and Shick, R. M.: Studies in Cerebrovascular Disease: III. The Use of Anticoagulant Drugs in the Treatment of Insufficiency or Thrombosis Within the Basilar Arterial System, *Proc. Staff Meet. Mayo Clin.* 30:116-126 (March 23) 1955.
5. Wright, I. S., and McDevitt, E.: Cerebral Vascular Diseases: Their Significance, Diagnosis and Present Treatment, Including the Selective Use of Anticoagulant Substances, *Ann. Int. Med.* 41:682-698 (Oct.) 1954.
6. Askey, J. M., and Cherry, C. B.: Thromboembolism Associated with Auricular Fibrillation: Continuous Anticoagulant Therapy, *J. A. M. A.* 144:97-100 (Sept. 9) 1950.
7. Luckey, E. H., in discussion on Luckey, E. H.: Cerebral Vascular Diseases, Transactions of a Conference Held Under the Auspices of the American Heart Association, Princeton, N. J., Jan. 24-26, 1954, I. S. Wright, Chairman, New York, Grune & Stratton, Inc., 1955, pp. 150-151.
8. Stürup, H., and Fog, T.: Antikoagulationsbehandling ved apoplexia cerebri: om differentialdiagnosen mellem haemorrhagia og encefalomalacia cerebri, *Nord. med.* 50:1261-1268 (Sept. 10) 1953.
9. Duff, I. F.: Effectiveness of Anticoagulant Therapy as Observed in 303 Cases, *Angiology* 1: 170-193 (April) 1950.
10. MacMillan, R. L., and Brown, K. W. G.: Haemorrhage in Anticoagulant Therapy, *Canad. M. A. J.* 69:279-283 (Sept.) 1953.
11. Fisher, M. and Adams, R. D.: Observations on Brain Embolism with Special Reference to the Mechanism of Hemorrhagic Infarction, *J. Neuropath. & Exper. Neurol.* 10:92-94 (Jan.) 1951.
12. Hicks, S. P., and Black, B. K.: Relation of Cardiovascular Disease to Apoplexy: A Review of 155 Cases with Autopsy, *Am. Heart J.* 38: 528-536 (Oct.) 1949.
13. Blumgart, H. L.; Freedberg, A. S.; Zoll, P. M.; Lewis, H. D., and Wessler, S.: The Effect of Dicumarol on the Heart in Experimental Acute Coronary Occlusion, *Tr. A. Am. Physicians* 60: 227-231, 1947.
14. Moyes, P. D.; Millikan, C. H.; Wakim, K. G.; Sayre, G. P., and Whisnant, J. P.: Influence of Anticoagulants on Experimental Canine Cerebral Infarcts, *Proc. Staff Meet. Mayo Clin.* 32:124-130 (March 20) 1957.
15. Whisnant, J. P.; Millikan, C. H.; Wakim, K. G., and Sayre, G. P.: Experimental Production of Cerebral Infarction in Animals, *Proc. Staff Meet. Mayo Clin.* 29:613-617 (Nov. 24) 1954.
16. Hurn, M.; Barker, N. W., and Magath, T. B.: Determination of Prothrombin Time Following the Administration of Dicumarol, 3,3'-Methylenebis (4-Hydroxycoumarin), with Special Reference to Thromboplastin, *J. Lab. & Clin. Med.* 30:432-447 (May) 1945.
17. Hill, N. C.; Millikan, C. H.; Wakim, K. G., and Sayre, G. P.: Studies in Cerebrovascular Disease: VII. Experimental Production of Cerebral Infarction by Intracarotid Injection of Homologous Blood Clot; Preliminary Report, *Proc. Staff Meet. Mayo Clin.* 30:625-633 (Dec. 28) 1955.

Obituaries

GILBERT HORRAX, M.D.

1887-1957

Dr. Gilbert Horrax, one of the most beloved and distinguished neurosurgeons of his generation, died Sept. 28, 1957, at the age of 70, after a brief illness.

He was born in Glen Ridge, N. J., the son of an English-born merchant and a New England mother whose family name was Gilbert. He graduated from Williams College with an A.B. degree in 1909, and his record there reflects his athletic ability and his popularity in the student body. His college in 1936 bestowed on him an honorary doctorate degree in further recognition of his accomplishments. After his graduation in medicine from Johns Hopkins in 1913, he joined the medical migration from Baltimore to Boston and in the next four years served as intern and assistant resident in surgery at the Peter Bent Brigham Hospital, as Arthur Tracey Cabot Fellow at the Harvard Medical School, and as resident surgeon at the Massachusetts General Hospital.

During World War I he was a member of the Fifth Base Hospital unit, which saw two years of unusually active service in a busy sector in France, and he was discharged with the rank of major. His wartime experience was nearly wholly with head injuries, and his achievements are fully apparent in Cushing's "From a Surgeon's Journal."

On his return to civilian life he became assistant professor of surgery at Harvard, and the able assistant and associate of Harvey Cushing at the Peter Bent Brigham Hospital until the latter retired, in 1932. The neurosurgery performed at the Brigham Hospital in those years was nearly wholly for brain tumors, and it was arduous work. There is no doubt that Cushing relied in large measure on Horrax' energy, dependability, and proficiency in the success of those busy years.

In 1932 Horrax joined the Lahey Clinic for the stated purpose of trying to see whether a neurosurgical service could be developed in that clinic. The prodigious growth of neurosurgery there under his direction, as well as the excellence of the work, has done much to advance and broaden the specialty in the last twenty-five years. Moreover, the Clinic came to be a veritable mecca where young men came to perfect their training.

His writings are contained in over one hundred publications, and his eminence has been recognized by membership in the principal surgical and neurological societies in this and in other countries. He served as president of the Society of Neurological Surgeons and as vice-president of the American Neurological Association and of the Association for Research in Nervous and Mental Disease.

A host of confreres, patients, and friends, both inside and outside medical circles, will feel the loss of this accomplished, modest, kindly, and gentlemanly physician.

BRONSON S. RAY, M.D.

Abstracts from Current Literature

Anatomy and Embryology

EDITED BY DR. BERNARD J. ALPERS

VERTEBRAL NERVE AND PLEXUS. H. H. HOFFMAN and A. KUNTZ, *A.M.A. Arch. Surg.* 74: 430 (March) 1957.

The vertebral nerve lies at the dorsal aspect of the vertebral artery. It is formed by rami from the stellate and intermediate cervical ganglia and has connections with all cervical nerve roots and the plexus of the vertebral artery. The vertebral nerve contains a few preganglionic fibers, which synapse with ganglia scattered within its course and in the vertebral plexus. Most of the fibers of the vertebral nerve are postganglionic connections with the cervical nerves. No complete sympathetic denervation of the head, neck, and upper extremity can be achieved without interruption of the vertebral nerve.

LIST, Grand Rapids, Mich.

CEPHALIC SYMPATHETIC NERVES. A. KUNTZ, H. H. HOFFMAN, and L. M. NAPOLITANO, *A.M.A. Arch. Surg.* 75:108 (July) 1957.

The internal and external carotid nerves and plexuses represent the major cephalic extension of the sympathetic thoracolumbar system. They contain ganglia in variable numbers and sizes. Most of the fibers are efferent fibers from the superior cervical sympathetic trunk, but the internal carotid nerve contains also efferent fibers from other sources. Furthermore, both the internal and the external carotid plexus carry afferent fibers to cranial and cervical nerves. In the cat, section of the cervical sympathetic trunk caudal to the superior cervical ganglion produces degeneration of the preganglionic fibers in the internal carotid nerve; interruption of connections between the ganglion nodosum and the sympathetic trunk causes additional degeneration of afferent fibers of vagal origin. Extirpation of the superior cervical sympathetic ganglion interrupts most of the cephalic sympathetic supply, but in order to obtain complete denervation of the head, all cervical and the upper two thoracic ganglia must be removed.

LIST, Grand Rapids, Mich.

BLOOD SUPPLY OF THE PRIMATE STRIOPALLIDUM. F. A. METTLER, H. R. LISS, and G. H. STEVENS, *J. Neuropath. & Exper. Neurol.* 15:377 (Oct.) 1956.

From studies on chimpanzees in which various branches of the internal carotid artery were occluded, the authors conclude that the perforating rami of the middle cerebral artery supply the caudate nucleus and putamen, as well as the outer segment of the globus pallidus, and, thus, that the designation "lenticulostriate" for such vessels is appropriate and should be retained.

SIEKERT, Rochester, Minn.

SPINAL AFFERENTS TO THE TRIGEMINAL SENSORY NUCLEI AND THE NUCLEUS OF THE SOLITARY TRACT. G. F. ROSSI and A. BRODAL, *confinia neurol.* 16:321, 1956.

Rossi and Brodal have demonstrated spinal afferents to the trigeminal sensory nuclei and to the nucleus of the solitary tract in cats. After differential spinal cord sections, degenerations of terminal fibers in brain stem nuclei were studied, using the silver impregnation method of Gleebs. The terminal degenerations found were of the same type as those which occur in the same nuclei following lesions of the cerebral cortex.

Spinal afferents to the sensory trigeminal nuclei and the nucleus of the solitary tract come from thoracic, and even lumbar, segments. They ascend in the ventrolateral funiculus, most of them probably in the ventral funiculus, and are both crossed and uncrossed. At least some of the fibers ending in the trigeminal nuclei ascend in the spinal tract. The route for the fibers to the nucleus of the solitary tract appears to be more medially situated and probably follows the medial bundle of the spinoreticular fibers.

Rossi and Brodal point out that these nuclei also receive corticofugal fibers and argue that they are not to be considered as simple relay stations.

FOLEY, Boston.

Physiology and Biochemistry

HYPERCALCIURIA FOLLOWING POLIOMYELITIS: ITS RELATIONSHIP TO SITE AND DEGREE OF PARALYSIS. M. F. DUNNING and F. PLUM, A. M. A. Arch. Int. Med. 99:716 (May) 1957.

The concept that demineralization of bone with resultant hypercalciuria and urinary calculus formation in paralytic disease is attributable to the degree of immobilization produced is challenged by this serial study of the urinary calcium, phosphorus, and creatinine excretion of a group of 27 patients with paralytic poliomyelitis. All of these patients exhibited a significant immediate elevation of urinary calcium, which became maximal by the 2d to the 8th week, regardless of the site or degree of paralysis (and consequent immobilization), although the more extensively paralyzed patients maintained the hypercalciuria over a longer period (12 months or more for quadriplegics) than did the less severely affected patients (4 to 6 months for ambulatory bulbar patients). The role of immobilization is further obscured by the evidence that mobilization, while reversing or preventing demineralization in healthy volunteers, may actually increase the urinary calcium excretion in patients with poliomyelitis. The presence of systemic neurohumoral factor(s) responsible for osseous demineralization is suggested on the basis of evidence of demineralization in other diseases of the nervous system, for example, meningeal tuberculosis, as well as the presence of elevated urinary 17-ketosteroids in patients with acute poliomyelitis having hypercalcemia and hypercalciuria.

PARSONS, Montrose, N. Y.

CARBOHYDRATE METABOLISM IN BRAIN DISEASE: X. LACK OF EFFECT OF CHLORPROMAZINE AND RESERPINE ON ABNORMAL CARBOHYDRATE METABOLISM IN CHRONIC SCHIZOPHRENIA. M. D. ALTSCHULE, R. M. GONCZ, and P. D. HOLLIDAY, A. M. A. Arch. Int. Med. 99: 892 (June) 1957.

The authors have reported altered intermediate carbohydrate metabolism (frequently poorly correlated with the clinical status) in schizophrenic subjects. In order to define more specifically the physiologic effect of tranquilizing agents on the schizophrenic process, a group of five female patients showing favorable psychiatric response to adequate courses of these drugs (reserpine and chlorpromazine) were studied from the standpoint of intermediate carbohydrate metabolism. In each of the five cases there was no correlation between the clinical improvement and the physiologic status, wherein the abnormalities in carbohydrate metabolism previously noted in schizophrenics were apparent. The authors conclude that these tranquilizing agents modify the symptoms of schizophrenia without altering the basic morbid process.

PARSONS, Montrose, N. Y.

INFLUENCE OF PROMAZINE AND METHYLPHENIDATE ON CEREBRAL HEMODYNAMICS AND METABOLISM. W. R. EHRLMANTRAUT, J. G. SHEA, H. E. TICKTIN, and JOSEPH F. FAZEKAS, A. M. A. Arch. Int. Med. 100:66 (July) 1957.

Twenty-one hospitalized convalescent nonpsychiatric patients were divided into three groups, the first of which was given intravenous promazine, the second intravenous methylphenidate, and the third promazine followed by methylphenidate. Cerebral blood flow studies were performed during control periods, as well as at an interval of 30 minutes following administration of drugs. Although the clinical effects of the drugs were characteristic (promazine, tranquilizing; methylphenidate, analeptic, with adequate reversal of promazine effects in Group 3), there was no alteration in cerebral blood flow (CBF) values. The authors suggest that promazine may exert its subcortical depressant through its inhibition of adenosinetriphosphate (ATP) system functioning in relation to the dephosphorylation processes, which are not of necessity associated with oxidative reactions. This would account for the clinical effect of promazine in the absence of changes in CMRO₂ (cerebral oxygen consumption in cubic centimeters per minute per 100 gm. of brain), as well as the antagonism for the former of methylphenidate—also without CMRO₂ changes.

PARSONS, Montrose, N. Y.

PERIODIC PARALYSIS ASSOCIATED WITH HYPERTHYROIDISM. E. L. OVERHOLD, VERNON M. SMITH, and E. D. WHITE, A. M. A. Arch. Int. Med. 100:132 (July) 1957.

The authors report the case of a 27-year-old white man who developed attacks of generalized weakness one month following the onset of symptoms of hyperthyroidism. The attacks were experimentally reproduced two hours following administration of oral carbohydrate (200 gm.), subcutaneous insulin (20 units), and 1:1000 epinephrine (0.5 cc.). They were aborted within three to four hours following administration of potassium chloride, intravenously (30 mEq.) and orally (62 mEq.). The attacks were not characterized by sensory or cranial nerve or intercostal muscle involvement. Hypokalemia and hypophosphatemia were present, with typical EKG change, consisting of development of U-waves at the end of the isoelectric T-wave. Following the attainment of a relatively euthyroid condition preparatory to surgery, the special low-carbohydrate-high-potassium diet was discontinued, whereupon a spontaneous attack of muscular weakness occurred. Following subtotal removal of a hyperplastic thyroid, no further attacks took place, and the previously mentioned techniques failed to evoke them. The mechanism whereby thyroxine predisposes to myoneural-junction potassium deficiency is not clear, but the authors stress the importance of the muscular paralysis as a manifestation of a number of conditions producing hypokalemia, including Conn's syndrome, conditions receiving desoxycorticosterone acetate (DOCA) therapy, chronic nephritis, acute diarrheas, and diabetic coma treated with insulin, as well as hyperthyroidism.

PARSONS, Montrose, N. Y.

DIABETES INSIPIDUS FOLLOWING HEAD INJURY. H. H. HIATT and S. LOWIS, A. M. A. Arch. Int. Med. 100:143 (July) 1957.

A 40-year-old man fell from a scaffolding, experiencing severe head trauma, and was admitted to the hospital in coma and quadriplegia. Eight days following the accident moderate diabetes insipidus developed with marked hyperchloremia and hypernatremia, all of which were corrected by the use of vasopressin tannate in oil (0.25 cc.). Despite this, episodes of vascular collapse with renal failure and pneumonitis led to the patient's death 23 days following the accident. The authors explain the electrolyte changes on the basis of damage to the posterior pituitary, resulting in insufficient output of antidiuretic hormone, impaired renal tubular absorption of water, and increased reabsorption of sodium chloride. This effect was readily reversed by posterior pituitary hormone. It is suggested that the complication of diabetes insipidus on the basis of derangement in posterior pituitary function should be suspected in more cases of head injury, as it is successfully treated by posterior pituitary hormone.

PARSONS, Montrose, N. Y.

A LONGITUDINAL STUDY OF THE BABINSKI AND PLANTAR GRASP REFLEXES IN INFANCY. H. F. DIETRICH, A. M. A. J. Dis. Child. 94:265 (Sept.) 1957.

Dietrich studied a group of infants from birth to the age of 2 years at regular intervals. He observed a spontaneously appearing Babinski sign in about half the group, principally in the neonatal period; it is not a reflection of clinically recognizable disease. A Babinski sign, often bilateral, is frequently, but irregularly, present in the first six months of life; thereafter it is relatively uncommon. Because the sign appears and disappears, sometimes repeatedly in the same infant, lack of myelination does not appear to be a rational explanation for its presence in the infant.

The plantar grasp reflex is usually present at or soon after birth. This sign is remarkably constant and disappears between 6 and 12 months of age, its disappearance being related to the age of standing.

SIEKERT, Rochester, Minn.

RENAL AND CEREBRAL HEMODYNAMICS WITH HYPOTENSION. A. E. PARRISH, J. KLAH, and J. F. FAZEKAS, Am. J. M. S. 233:35 (Nov.) 1957.

Simultaneous estimation of cerebral and renal hemodynamics was made during acute and prolonged hypotension induced in 12 patients with renal insufficiency by the administration of trimethaphan camphorsulfonate (Arfonad). The mean arterial pressure having been reduced 40%-50%, cerebral arteriovenous O₂ differences were measured after 2 to 9 minutes and then after 30 to 60 minutes. Simultaneous studies of renal function were made. The early effects of hypotension consisted in a cessation of urine flow and a widening of the cerebral

ABSTRACTS FROM CURRENT LITERATURE

arteriovenous differences. After 30-60 minutes, although urine flow had resumed, there was a reduction in urine flow, filtration rate, and cerebral vascular resistance but no change in cerebral blood flow or cerebral metabolic rate. It was inferred that, although both the kidney and the brain respond actively to hypotension with decreased flow, a prolonged reduction of blood pressure was followed by a compensatory maintenance of blood flow to the brain and kidneys in spite of a ganglionic-blocking agent and advanced vascular disease.

BERLIN, New York.

INCREASE IN TISSUE SEROTONIN FOLLOWING ADMINISTRATION OF ITS PRECURSOR 5-HYDROXYTRYPTOPHAN. S. UDENFRIEND, H. WEISSBACH, and D. F. BOGDANSKI, *J. Biol. Chem.* 224: 803, 1957.

5-Hydroxytryptophan is rapidly taken up by most tissues and converted to serotonin wherever 5-hydroxytryptophan decarboxylase is present. Brain levels of more than 10 times normal have been reached and maintained for several hours when it is administered. Laboratory animals show marked central nervous system disturbance, quite similar to the effects of the hallucinogenic drug lysergic acid diethylamide.

PAGE, Cleveland.

EFFECT OF 5-HYDROXYTRYPTAMINE ON THE UPTAKE OF P^{32} IN THE RAT. P. LINGJAERDE and O. E. SKAUG, *J. Biol. Chem.* 226:33, 1957.

The uptake of P^{32} was used as a measure of the rate of metabolic phosphorylation in rats injected intraperitoneally with serotonin. Increased uptake in the adrenal glands is explained as being due to the stressor action of serotonin, since it occurs in shock and trauma. No explanation was suggested for the decreased uptake of spleen and testis or for the increased uptake of pancreas, diaphragm, and liver. Since there was no change in brain uptake, it was concluded that serotonin either does not affect uptake or does not penetrate the blood-brain barrier.

PAGE, Cleveland.

THE INCORPORATION IN VIVO OF P^{32} -LABELED ORTHOPHOSPHATE INTO INDIVIDUAL PHOSPHATIDES OF RAT TISSUES. G. V. MARINETTI, R. F. WITTER, and E. STOTZ, *J. Biol. Chem.* 226:475, 1957.

Rats were used for the study of incorporation of P^{32} -labeled *o*-phosphate into phosphatides of different tissues. Lecithin, phosphatidyl ethanolamine, and a component behaving like inositol phosphatide were the major lipids and showed the greatest amount of labeling. The presence of as many as 15 labeled phosphatides in a single tissue shows how complex they are. The specific activity of brain was very low.

PAGE, Cleveland.

ON THE CONVERSION OF SQUALENE TO LANOSTEROL IN VITRO. T. T. TCHEN and K. BLOCH, *J. Biol. Chem.* 226:921, 1957.

Squalene is converted to either lanosterol or cholesterol by rat liver homogenates according to the way the homogenate is prepared. Hog liver homogenate can convert squalene only to lanosterol, the process requiring both the particulate and the soluble fractions of the homogenate. It is an aerobic process, requiring pyridine nucleotide.

PAGE, Cleveland.

ON THE MECHANISM OF ENZYMATIC CYCLIZATION OF SQUALENE. T. T. TCHEN and K. BLOCH, *J. Biol. Chem.* 226:931, 1957.

During the cyclization of squalene to lanosterol in a medium of D_2O , no proton or OH^- from the medium is incorporated into lanosterol, molecular oxygen is incorporated into lanosterol, and isoeuphol is not an intermediate. The results support the hypothesis of a concerted cyclization and establish molecular oxygen as the source of the hydroxyl group of lanosterol.

PAGE, Cleveland.

ON THE DEMETHYLATION OF LANOSTEROL TO CHOLESTEROL. J. A. OLSON JR., M. LINDBERG, and K. BLOCH, *J. Biol. Chem.* 226:941, 1957.

The demethylation of lanosterol to cholesterol requires both the particulate and the soluble fractions of liver homogenates. A more polar metabolite has been isolated from liver

homogenate incubated with lanosterol and semicarbazide which is an intermediate in the conversion of lanosterol to cholesterol. It is suggested that the 4,4-dimethyl and the 14-methyl substituents of lanosterol are oxidized and eliminated from the steroid skeleton by decarboxylation.

PAGE, Cleveland.

AN INORGANIC PYROPHOSPHATASE OF SWINE BRAIN. U. S. SEAL and F. BINKLEY, J. Biol. Chem. 228:193, 1957.

An inorganic pyrophosphatase has been concentrated from frozen swine brain. The preparation was free of adenosinetriphosphatase and alkaline phosphatase. The pH optimum was 7.6 to 7.8; it required magnesium ions and was activated by ethylenediaminetetraacetic acid, cysteine, glutathione, and thioglycolic acid. It was inhibited reversibly by several polyvalent metal ions and by *p*-chloromercuribenzoate. Activity seems dependent upon sulfhydryl groupings.

PAGE, Cleveland.

THE BIOSYNTHESIS OF BETA-HYDROXY-BETA-METHYLGLUTARIC ACID. H. RUDNEY, J. Biol. Chem. 228:363, 1957.

Rudney has shown that both animal and plant tissues synthesize branched chain fatty acids, such as β -hydroxy- β -methylglutaric acid from acetate. Liver microsomes contain the major part of the enzyme which forms this acid. The 4-carbon moiety, which condenses with acetyl CoA to form β -hydroxy- β -methylglutaric acid is acetoacetyl CoA and not free acetoacetate. Both β -hydroxy- β -methylglutaric and β -hydroxyisovaleric acid are presumed steroid precursors.

PAGE, Cleveland.

RHINENCEPHALIC ACTIVITY DURING THOUGHT. H. LESSE, R. B. HEATH, R. R. MONROE, and W. H. MILLER, J. Nerv. & Ment. Dis. 122:433 (Nov.) 1955.

Three schizophrenic patients and one with intractable pain were studied to ascertain the relationship of thought processes to electrical activity of the brain. Recording electrodes were stereotactically applied to the amygdala, anterior hypothalamus, septal area, tegmentum of the mesencephalon, and frontal and parietal areas of the cortex. The subjects were interviewed concerning topics of no significance or of special emotional significance. A change localized to the rostral hippocampal and amygdaloid areas occurred with the discussion of affectively significant topics. The change consisted of the appearance of bursts of 14-17 cps waves from the rostral hippocampus and of 20-30 cps waves from the amygdala, together with an increase in amplitude, lasting up to 20 minutes. Olfactory stimuli and suggestions that the subjects think of odors also elicited this change, but the changes were not related to the pleasantness or unpleasantness of the odor. The pattern of activity did not spread to other subcortical regions, nor was it reflected in cortical recordings. The rhinencephalic electrical activity was not correlated with overt expressions of emotion, nor was the characteristic change evoked by lysergic-acid-induced states of panic when the person's thinking was disorganized and she was unable to associate her fear with past experience.

BERLIN, New York.

PATHOLOGICAL LAUGHTER. W. E. STERN and W. J. BROWN, J. Neurosurg. 14:129 (March) 1957.

Abnormal laughter associated with involvement of the diencephalon by a neoplastic or vascular lesion has been noted by other investigators. Stern and Brown report the occurrence of laughter in a 39-year-old man who had an infiltrating glioblastoma multiforme involving the diencephalon and brain stem. The characteristic feature of this patient's laughter was the lack of affect and warmth of autonomic display that accompanies mirthful laughter. There was no massive excitation or spread of abnormal innervation. The episodes of laughter were abrupt in onset and cessation and of short duration. They were similar to an epileptic episode, although the patient was aware of the laughter and was not amnesic for the episode.

The authors believe that a diencephalomesencephalon-integrating system responsible for emotional expression may have been stimulated and subsequently paralyzed by the advancing tumor.

MANDEL, Philadelphia

ABSTRACTS FROM CURRENT LITERATURE

STUDIES IN HEADACHES: SUMMARY OF EVIDENCE CONCERNING A NOXIOUS AGENT ACTIVE LOCALLY DURING MIGRAINE HEADACHE. A. M. OSTFELD, L. F. CHAPMAN, H. GOODELL, and H. G. WOLFF, *Psychosom. Med.* 19:199 (May-June) 1957.

The thesis that during vascular headache of the migraine type there is elaborated locally in extracranial tissue through neuron activity, a tissue-damaging and pain-threshold-lowering agent is supported by the following evidence: (1) lowering of deep-pain threshold and appearance of edema in areas of the scalp experiencing a migraine headache; (2) vasodilatation of the bulbar conjunctiva on the side of the hemicrania, not modified by topical or parenteral antihistaminics or anticholinergic agents; (3) biopsy studies of temporal arteries removed when the vessels were involved in a migraine headache, showing perivascular edema fluid; (4) injection of hyaluronidase into a tender area of the head during a migraine attack, with fourfold increase in the area of tenderness; (5) increased amount of amino acids in extracranial tissue fluid removed from the sites of headache; (6) induction of erythema and slight decrease of the skin pain threshold on injection of this fluid into the skin; (7) capacity of the fluid to contract the uterus of a rat, and (8) production of hemicrania by the combination of temporal artery dilatation (by warm water) and injection of the tissue fluid periarterially when dilatation alone or fluid alone or dilatation and saline did not.

AIGNER, Rochester, Minn.

PATHOPHYSIOLOGY OF MYOTONIA CONGENITA (THOMSEN). P. STERN and N. ZEC, *Psychiat. et neurol.* 132:381 (Nov.-Dec.) 1956.

Stern and Zec proceed on the assumption that myotonia congenita represents not merely a disturbance in the function of the myoneural junction (which for somatic nerves is considered analogous to the extraneuraxial ganglia of the autonomic nervous system) but, rather (or additionally), a defect in the upper motor neuron system, wherein a reduction of its usual inhibitory influence gives rise to increased independent activity at the nerve endings, resulting in the characteristic symptoms. In order to shed further light on the pathophysiologic focus of myotonia, the authors produce an experimental myotonic syndrome in rats by the administration of 2,4-dichlorophenoxyacetate, after which a series of drugs acting in different ways on different portions of the nervous system was administered. Observations with respect to the effect of each upon the myotonic syndrome were then made. It was discovered that a curarizing agent (C10) and one resulting in local deficit of K ions (polyphenylethylene-sulfonic acid) both produced improvement of the myotonia, whereas "centrally" acting drugs, such as mephenesin (Tolserol) and chlorpromazine, aggravated the condition. The authors consider that these findings "localize" the pathophysiology of myotonia to the "end-plate," and they then go on to speculate upon a "centripetal" influence on the neuraxis. It is unlikely that such precision of localization could be achieved by noting either the effect of any distal blocking agent on a syndrome whose major feature is overactivity of the effector organ, or the effect upon such a syndrome of the administration of a drug such as chlorpromazine, whose mode and site of action are, as yet, largely undetermined.

PARSONS, Montrose, N. Y.

SPONTANEOUS AND INDUCED CONVULSIONS IN UNILATERAL DISEQUILIBRIUM. L. HALPERN, *Psychiat. et neurol.* 133:29 (Jan.-Feb.) 1957.

Halpern reports the case of a 41-year-old woman with a right-sided sensorimotor induction syndrome secondary to meningoencephalitis, in which spontaneous or induced lateral deviation of both right extremities resulted in a convulsion, characterized by predominantly homolateral adverse tonic spasms of the involved side (eyes, head, body) and clouding, but not complete loss, of consciousness. The interseizure electroencephalogram showed diffuse symmetrical slow activity, and no changes were noted during attacks. A second patient, with a left-sided disequilibrium and similar convulsions, associated with profound loss of consciousness, evidenced at all times a normal electroencephalogram. In both instances blindfolding the patient prevented the attack, and the facility with which the latter was elicited was noted to be inversely proportional to the amount of visual stimulation presented. The relationship between the sensorimotor induction features and convulsions was particularly evident in the case of the second patient, in whom these features simultaneously disappeared after an attack of hepatitis. The authors liken the seizures to movements seen in tonic neck reflexes and attribute them to the effect of mutual motor influence of changed position of the extremities, which, in unilateral disequilibrium, results in extensive disintegration of kinetic automatisms occurring at midbrain or diencephalic levels.

PARSONS, Montrose, N. Y.

THE PEDUNCULUS CEREBRI OF THE CAT. K. MECHELSE, *Psychiat. et neurol.* 133:257 (May) 1957.

Study of serial sections of the internal capsule and cerebral peduncle of the cat by the Haggqvist stain and fiber-count technique was undertaken three weeks following the production of experimental cortical and thalamic lesions, with the object of determining the distribution of various contingents through analysis of fiber-size patterns. It was found that the fiber patterns containing maximal numbers of fibers of a certain size were specific for the given portion of the cerebral cortex from which these corticofugal fibers originated. Fiber systems connecting cortex and thalamus and various striatopallidal structures in the internal capsule were readily differentiated from other corticofugal fibers passing farther caudally into the cerebral peduncle. In the cerebral peduncle a specific fiber-pattern arrangement was encountered, the larger fibers from primary sensory-motor areas lying between medially oriented frontopontine and laterally oriented temporo- and parietopontine fasciculi. Comparison of these results with those of previous similar studies on monkeys disclosed differences, notably in the direction of greater contribution of sensory areas to the large-fiber group comprising the middle peduncular constituent in the cat; in the monkey and, presumably, in man this is essentially composed of elements arising from the motor cortex.

PARSONS, Montrose, N. Y.

CEREBRAL METABOLISM DURING ELECTRICALLY INDUCED CONVULSIVE ACTIVITY AND PETIT MAL ATTACKS. H. HEYCK, *Psychiat. et neurol.* 133:346 (June) 1957.

Heyck reports the cases of two female patients with readily elicited petit-mal electroencephalographic patterns in whom associated indication of cerebral metabolic activity was obtained by determination of the cerebral arteriovenous oxygen difference during the appearance of petit mal patterns, elicited in one instance by pentylenetetrazol and in the other by photic stimulation. Despite the fact that increases in AVO₂ difference occurred in the first case (correlated with administration of both the pentylenetetrazol and subsequent sedative), it was concluded that no reliable indication of the level of cerebral metabolism is furnished by the electroencephalogram. Whatever alterations in cerebral metabolism take place during a generalized seizure would appear to be a consequence of the anoxemia attendant upon temporary circulatory readjustments, such as vasoconstriction and arteriovenous shunts.

PARSONS, Montrose, N. Y.

Neuropathology

RHABDIOMYOSARCOMA OF THE CEREBELLUM. J. L. DE FARIA, A. M. A. Arch. Path. 63:234 (March) 1957.

The tumor described by de Faria involved the left cerebellar hemisphere of a 52-year-old woman. It measured 5 cm. in diameter, was firm and solid, and distorted the hemisphere. It was covered by leptomeninges but was not attached to the dura. Microscopically, some areas revealed a myxomatous pattern with stellate cells embedded in a loose syncytium, whereas others were distinctly fibrosarcomatous. A third pattern consisted of elongated and conspicuous bundles of cells with abundant eosinophilic cytoplasm. Some of the last-mentioned cells possessed longitudinal striations, and others were typically cross striated. The striations were apparent both in hematoxylin-eosin and Mallory's phosphotungstic-acid-hematoxylin preparations. There were many tumor giant cells.

AFONTE, Guam, Mariana Islands.

XANTHOMATOSIS OF THE NERVOUS SYSTEM. I. Feigin, *J. Neuropath. & Exper. Neurol.* 15: 4006 (Oct.) 1956.

Feigin reports two cases of xanthomatosis of the nervous system. The first was that of a 10-year-old boy who had an illness of two and one-half years' duration, characterized by skin lesions, lymphadenopathy, diabetes insipidus, obstructive jaundice, splenomegaly, and headache. A generalized lipogranulomatous (Schüller-Christian) involvement of visceral organs was observed at necropsy. Within the brain were noted focal nodules of similar character, the nodules consisting of a central granulomatous area, with dense collagen fibers and moderate cellular infiltration of xanthoma cells and ordinary phagocytes, and a peripheral portion, containing few collagen fibers and characterized by large mononuclear cells, resembling phagocytes, and a moderate number of characteristic xanthoma cells.

ABSTRACTS FROM CURRENT LITERATURE

The second case was that of a girl, aged 11 years, who developed signs of cord damage four days after the disappearance of the rash of a febrile illness presumed to have been measles (postinfectious encephalomyelitis). The clinical signs of cord damage progressed for a week and resulted in paraplegia. Death occurred four and one-half months later. Necropsy revealed the medulla and spinal cord to be severely damaged and infiltrated with cells containing xanthomatous material. In only one small area in the centrum ovale was there a lesion of perivenous demyelination.

Feigin recalls that in many cases of xanthomatosis demyelination has been reported. The second case is the reverse and, to him, suggests that a relationship may exist between xanthomatoses and demyelinating diseases.

SIEKERT, Rochester, Minn.

THE INCIDENCE, COMPOSITION, AND PATHOLOGICAL SIGNIFICANCE OF INTRACEREBRAL VASCULAR DEPOSITS IN THE BASAL GANGLIA. V. T. SLAGER and J. A. WAGNER, *J. Neuropath. & Exper. Neurol.* 15:417 (Oct.) 1956.

Slager and Wagner studied one coronal section, 75 mm. in thickness, from each of 200 brains, the rostral limit being through the optic chiasm and anterior commissure. Basophilic deposits were found in two-thirds of the slices, chiefly in the globus pallidus. They consist of an acid mucopolysaccharide ground substance containing iron, but rarely calcium. The authors feel the deposits are vascular rather than neural in origin. A definite increase in incidence occurs with increasing age.

SIEKERT, Rochester, Minn.

MALFORMATION OF THE ADULT BRAIN (ALBINO RAT) RESULTING FROM PRENATAL IRRADIATION. H. E. RIGGS, J. J. McGRATH, and H. P. SCHWARZ, *J. Neuropath. & Exper. Neurol.* 15:432 (Oct.) 1956.

Irradiation during fetal life (5-9 days before birth; 13-17 days after mating) produced in the adult rat a pattern of related structural deformities limited to the telencephalon. Dystrophic development of the neocortex appeared to provide the basis for the anomalous growth. While the deformities were not stereotyped, the degree of abnormality was correlated with the extent of heterotopic neopallial growth. The basic features were present at birth.

The degree of deformity could not be closely correlated with the stage of fetal development at the time of the exposure, since minimal as well as extensive malformation occurred after irradiation on any of the five successive days.

SIEKERT, Rochester, Minn.

INFANTILE SUBACUTE NECROTIZING ENCEPHALOPATHY WITH PREDILECTION FOR THE BRAIN STEM. R. B. RICHTER, *J. Neuropath. & Exper. Neurol.* 16:280 (July) 1957.

Richter reports the cases of three infants who presented similarities suggestive of a diffuse brain disease that was progressive and fatal. The chief clinical features of the cases were (1) early appearance, (2) inadequate sucking reflexes and regurgitation, (3) persistence of feeding difficulties associated with dysphagia, (4) slowness or lack of behavioral development, (5) eventual deterioration of sensorimotor ability, (6) impaired or absent pupillary light reflexes, (7) evidence of blindness or deafness, (8) hyperreflexia and extensor plantar reflexes, and (9) late convulsions.

The brains of all infants contained foci of necrosis of the brain stem, which affected the ground substance in both gray and white matter. In two cases the necrosis exceeded the limits of the brain stem and included the deep gray masses of the cerebral hemispheres and the cerebral and cerebellar cortex. The involvement of the ground substance revealed often symmetrical changes varying from defective staining to rarefaction. The other outstanding findings were hypervascularity of the capillaries, proliferation of the astrocytes and microglia, remarkable preservation of the neurons in areas otherwise completely destroyed, and predominant selectivity of the gray matter by the destructive process.

The author found four other cases in the literature with similar clinical and pathologic changes bringing the total number of cases to seven. He suggests an exogenous toxin as the cause, since he was able to produce similar changes in monkeys by intoxication with quinoline. It is felt this encephalopathy is not a form of Wernicke's disease but may be of the same general nature.

AIGNER, Rochester, Minn.

DEGENERATIVE ENCEPHALOPATHY OF CHILDHOOD (CORTICAL DEGENERATION, CEREBELLAR ATROPHY, CHOLESTERINOSIS OF BASAL GANGLIA). G. A. JERVIS, J. Neuropath. Exper. Neurol. 16:308 (July) 1957.

Jervis reports the case of a girl who, following a normal development to the age of 15 months, showed progressive mental deterioration and spasticity of all extremities, leading to death at the age of 5 years. Pathologically, three main features were present: (1) extensive cortical degeneration, found mostly in the superficial layers of the cortex, in contrast to the cases described by Ford as "familial degeneration of the cerebral gray matter in children," in which the deep cortical layers bore the brunt of the pathological changes; (2) atrophy of the cerebellum, involving the cortex, Purkinje cells, and granules, and (3) extensive lipid deposits in the basal ganglia, which were shown to be chiefly cholesterol.

It is the author's opinion that the clinical picture and some of the pathological features of the case were similar to Alper's "diffuse progressive degeneration of the gray matter of the cerebrum," whereas the lesions of the basal ganglia were akin to a certain form of van Bogaert's cerebral cholesterolinosis. The pathological picture as a whole conforms to no known syndrome.

AIGNER, Rochester, Minn.

PRIMARY INTRACRANIAL NEOPLASMS: PROGNOSIS AND CLASSIFICATION OF 513 VERIFIED CASES. K. M. EARLE, E. H. RENTSCHLER, and S. R. SNODGRASS, J. Neuropath. & Exper. Neurol. 16:321 (July) 1957.

The authors review the histological classification in a large group of unselected primary intracranial neoplasms on the basis of clinical behavior. Among 46,730 surgical specimens and 9,720 autopsies in the 62 years from 1892 to 1954 there were found to be 513 primary intracranial neoplasms. Only 115 had been seen prior to 1940. All the slides in the cases were restudied and reclassified according to schemes of Bailey, Penfield, and Kernohan. The clinical records were studied with special reference to duration of preoperative symptoms and postoperative survival.

For the astrocytic glioma group, only three categories, instead of the usual four, were distinguished: (1) glioblastoma multiforme (32%), with a postoperative survival of six months; (2) astrocytomas, well-differentiated (12%), with a postoperative survival of 44 months, and (3) astrocytoma, poorly differentiated (9%), with a postoperative survival of 23 months. These three groups, plus meningiomas (15%), glioma unclassified (5%), medulloblastoma (5%), neurilemoma (4%) and pituitary adenoma (5%), represented 89% of the cases. It was felt that the increasing age of our population may have accounted for the increased incidence of glioblastomas.

Location of the slowly growing neoplasms was the determining factor in prognosis more frequently than histologic type.

AIGNER, Rochester, Minn.

A CASE OF INTRAMEDULLARY SHEATH CELL TUMOR OF THE SPINAL CORD: CONSIDERATION OF VASCULAR NERVES AS A SOURCE OF ORIGIN. H. E. RIGGS and W. U. CLARY, J. Neuropath. & Exper. Neurol. 16:332 (July) 1957.

Riggs and Clary report an intramedullary sheath-cell tumor of the spinal cord. The patient was a 60-year-old Negro man with a three-year history of progressive numbness of the hands and feet, associated with stiffness to the point of being unable to walk during the past year. Atrophy of the hand and shoulder muscles was noted, associated with fasciculations. The reflexes were generally exaggerated, and Hoffmann and Babinski signs were positive. Bilateral spasticity was present in all limbs, being most marked in the legs. A sensory disturbance to pain and temperature was found in the C-4 and C-5 dermatomes. A spinal tap was normal, and a myelogram revealed a block at C-3 and C-5. A laminectomy was unrevealing, and the patient's neurological status remained unchanged except for progressive atrophy and incontinence. He died two years later.

Autopsy revealed a small, discrete tumor embedded in the central portion of the cord at the fourth and fifth cervical segments. Microscopic sections revealed architectural and cytological characteristics of a tumor of the nerve sheath. Nerve plexuses accompanying intrinsic arteries of the cord are suggested as a possible origin of such tumors. The authors selected at random 36 cases of spinal cord sections, and they found well-developed nerve plexuses on the intrinsic ramifications of the spinal arteries in 14 cases.

AIGNER, Rochester, Minn.

ABSTRACTS FROM CURRENT LITERATURE

ONE HUNDRED INTRACRANIAL MENINGIOMAS FOUND INCIDENTALLY AT NECROPSY. M. W. WOOD, R. J. WHITE, and J. W. KERNOHAN, *J. Neuropath. & Exper. Neurol.* 16:337 (July) 1957.

Three hundred asymptomatic and unsuspected, and hence undiagnosed, brain tumors were found at the Mayo Clinic from 1939 to 1954. One hundred of these were meningiomas, representing 10.3% of all brain tumors, both symptomatic and asymptomatic, found at necropsy during this time.

Incidental meningiomas were found in a 1:1 sex ratio and occurred most frequently in the seventh and eighth decades of life. The average age was 69.8 years. In 16% of cases the tumors were multiple. The distribution revealed several sites of predilection—30.5% were parasagittal; 24.6% were over the free convexity; 16.2% were over the sphenoid ridge; 12.7% were in the supra- or intrasellar region; 9.2% were in the posterior fossa (half of these were in the cerebellopontine angle), and 6.8% were in the basifrontal region or in the olfactory groove.

The sizes of the meningiomas varied—61% were 1 cm. or less; 22% were between 1 and 2 cm., and only two were larger than 5 cm. one being 7.5 cm. in its longest diameter.

By histologic examination, 86% were classified as meningotheliomatous tumors, 10% as psammomatous tumors, and 4% as fibroblastic meningiomas.

AIGNER, Rochester, Minn.

HISTOPATHOLOGY OF MENINGO-FACIAL ANGIOMATOSIS (STURGE-WEBER'S DISEASE). F. J. WOHLWILL and P. I. YAKOVLEV, *J. Neuropath. & Exper. Neurol.* 16:341 (July) 1957.

Wohlwill and Yakovlev report four cases of Sturge-Weber disease. Outstanding findings in this series of cases was the polymorphism of the histological changes in the malformed blood vessels in different cases and in different organs of the same case. No true angiomas were found in the cerebral substance itself in any of the cases, although the cortical and subcortical white matter revealed a conspicuous overgrowth of arteries and veins.

The malformed vessels, which were mostly veins, revealed frequently thickened walls of hyalinized connective tissue, in which the smooth muscle and elastic fibers were absent or fragmented. Lime salts were also frequently found deposited in the vessel walls.

The gyri supplied by the involved vessels revealed pathological changes secondary to the circulatory disturbance and ischemia. These consisted of diffuse atrophy, degeneration of nerve cells, cell loss, glial proliferation, and marginal gliosis. Also present were deposits of a hematoxylinophilic substance; some were present as fine granules in the capillary walls, and others were larger deposits, bearing no relation to the vessel. Attempts to identify the material were inconclusive. In addition to the hematoxylinophilic substances, round, light-refracting psammoma bodies (corpora arenacea) were present in great numbers in structures in which they are ordinarily rare, such as the Gasserian ganglion, dorsal roots, and dura. Anomalies of architecture of the central and peripheral components of the nervous system were present, which were clearly of a developmental histogenic type. In the viscera, angiomas were found also in the lungs, intestine, and ovary.

AIGNER, Rochester, Minn.

SYRINGOMENCEPHALIA: REPORT OF A CASE WITH SIGNS OF PARKINSON'S DISEASE HAVING A SYRINX OF THE SUBSTANTIA NIGRA. R. C. HARDY and L. D. STEVENSON, *J. Neuropath. & Exper. Neurol.* 16:365 (July) 1957.

Hardy and Stevenson report a case of syringomencephalia in a 60-year-old man, who had a right-sided tremor of five-years' duration. Examination revealed also slight rigidity of the right arm. The neurological state was otherwise negative.

Autopsy revealed the substantia nigra on the left to be reduced greatly in size and to be replaced by long, narrow cavities. Microscopically, these were seen to be surrounded by glial tissue and lined with ependymal cells.

AIGNER, Rochester, Minn.

DEGENERATION OF THE SPINAL CORD DUE TO VITAMIN B₁ AND/OR PHOSPHORUS DEFICIENCY AND TO LESIONS OF THE GASTRIC MUCOSA IN ALBINO RATS. T. LEHOCZKY and J. SÓS, *J. Neuropath. & Exper. Neurol.* 16:371 (July) 1957.

Lehoczky and Sós report the results of experimental studies in animals in an attempt to answer the problem of myelopathy in humans not due to pernicious anemia.

Histological changes were observed in five groups of 40 albino rats and in 34 control animals. The five groups were treated as follows: 1. Ten animals were subjected to extirpation of the gastric mucosa. Six weeks later five spinal cords were normal and five others displayed only minor pathologic changes. 2. Thirteen animals were fed a thiamine-deficient diet after extirpation of the gastric mucosa. In all animals the spinal cords showed marked lesions with all staining methods employed. 3. Seven animals were fed thiamine-deficiency diets only. The lesions of the cords were essentially the same as in group 2. 4. In view of the significant part played by phosphorylation in the chemistry of thiamine, five animals were fed on a diet poor in phosphorus. Although the rats appeared to be in perfect health, the spinal cords revealed changes similar to Groups 2 and 3, but of a milder nature. 5. Five animals were fed diets with lack of phosphorus plus thiamine deficiency. Myelopathic degeneration was severe in this group.

AIGNER, Rochester, Minn.

ENZYMATIC ACTION OF FLUIDS FROM CYSTIC BRAIN TUMORS: II. M. SPIEGEL-ADOLPH and H. T. WYCIS, *J. Neuropath. & Exper. Neurol.* 16:404 (July) 1957.

The fluids of 15 cystic tumors of the brain were examined for their enzymatic action. In the glioma group parallelism was found to exist between enzymatic action against deoxyribonucleic acid and histological findings—i. e., the more undifferentiated the tumor, the more pronounced was the enzymatic activity. With craniopharyngiomas the enzymatic activity increased with clinical deterioration and disappeared after successful therapy with radioisotopes. Fractionation of the cystic fluids was attempted by ultrafiltration and neutral salt solution. The results seemed to point toward a possible diagnostic and prognostic application.

AIGNER, Rochester, Minn.

CHRONIC PORTO-HEPATIC ENCEPHALOPATHY. M. A. BALTZAN, J. OLSZEWSKI, and N. ZERVAS, *J. Neuropath. & Exper. Neurol.* 16:410 (July) 1957.

The authors report the case of a 54-year-old white man with chronic progressive pyramidal, cerebellar, and cerebral involvement and associated liver disease. The pathologic diagnosis was thrombosis of the portal vein with the development of a portohepatic shunt. Spongy degeneration with formation of Alzheimer glia cells was seen in the cortex, dorsal putamen, inner portion of the pallidum, red nucleus, brachium conjunctivum, and zona incerta. Copper metabolism was found to be normal.

This case is compared with other cases from the literature, and it is concluded that the neuropathologic changes may be the result of intoxication by portal blood which by-passes the liver and fails to be detoxified there. Ammonia is considered as a possible intoxicant. Since the changes in this process and Wilson's disease are similar, and since in this case the copper metabolism is normal, it is suggested that the neuropathologic changes of Wilson's may be related to portohepatic abnormalities, and not directly to the toxic effect of copper.

AIGNER, Rochester, Minn.

CEPHALIC BRUITS IN CHILDREN. H. W. DODGE JR., *J. Neurosurg.* 13:527 (Nov.) 1956.

Dodge reviews previous reports on cephalic bruits in children and states that in a neurologically normal infant showing adequate development a cephalic bruit probably has no significance. Anemia is frequently a contributing factor in the production of a bruit; but if an intracranial bruit is heard in the presence of a normal hemoglobin, other causes should be investigated. Dodge emphasizes the importance of examining for a bruit, since this is an oft-neglected part of the neurological examination.

MANDEL, Philadelphia

INVESTIGATION OF DEMYELINATING DISEASES AND QUANTITATIVE DETERMINATION OF "MYELIN LIPIDS." G. W. F. EDGAR, *Psychiat. et neurol.* 131:274 (May-June) 1956.

Edgar believes that multiple sclerosis and diffuse sclerosis constitute reactions of adult and infant brain tissue, respectively, to the same pathogen, the primary histologic features of which are sharply delineated areas of demyelination with relative preservation of axis cylinders, anisomorphic gliosis, and associated "symptomatic inflammatory reactions." Since the available myelin stains give little information as to the physicochemical factors involved in demyelination, it is suggested that the nature of the unknown pathogen peculiar to these two diseases may be better understood by investigating chemical abnormalities of the demyelinated tissue. One of these is a study of the ratio of free and esterified cholesterol (the latter appearing in early Wallerian degeneration and in several cases of multiple and diffuse

ABSTRACTS FROM CURRENT LITERATURE

sclerosis). Another is the "sphingolipid index," the expression of the relationship of glycosphingosides to total sphingolipids; the importance of these substances is emphasized by their relatively (gangliosides excepted) sharp localization to white matter and their concentration differential in various portions of the central nervous system, with contrasting rates of increase with age. The above determinations may be performed in the routine examination of the recently autopsied brain upon carbon dioxide-frozen sections. The conduct of certain other research projects, including investigation of proteolipids, the hexose fraction of the glycosphingosides, cephalin, altered gangliosides, and the separation and identification of fatty-acid components of sphingolipids, involves the use of neurochemical laboratory facilities.

PARSONS, Montrose, N. Y.

PATHOLOGY OF BALLISMUS. A. JUBA, *Psychiat. et neurol.* 134: (Aug.) 1957.

Juba reports the pathologic findings in the case of a 43-year-old woman who, at the age of 37, developed a bilateral choreoballismus syndrome, variously diagnosed as hepatolenticular degeneration and Huntington's chorea. Pathological changes included focal vascular lesions of the neostriatum and pallidum. The chorea and ballismus were explained on the basis of secondary degeneration of pallidosubthalamic pathways. Study of these changes enabled the author to trace the connections of the subthalamus. Afferent pathways from both pallidum and contralateral corpus Luysii, as well as efferent fibers to pallidum, red nucleus, substantia nigra, and, possibly, the thalamus, were demonstrated. It is suggested that ballismus may be produced not only by lesions of the subthalamus but also by involvement of pallidosubthalamic fiber tracts.

PARSONS, Montrose, N. Y.

Psychiatry and Psychopathology

CASE STUDIES IN CEREBRAL ANOXIA: XI. SIGNIFICANCE OF FOCAL VASCULAR LESIONS IN THE BASAL GANGLIA IN A CASE OF SEVERE ASTHMA. C. B. COURVILLE, *Bull. Los Angeles Neurol. Soc.* 21:90 (June) 1956.

Courville reports the case of a 54-year-old patient with chronic asthma who died of renal and cardiac failure after having had two episodes of severe respiratory embarrassment.

From a pathological standpoint, old and recent focal lesions in the striatum were found which consisted of recent areas of softening with glial-cell infiltration and recent areas of hemorrhagic infarction. There was a patchy loss of cells in the frontal cortex. There was little evidence of vascular disease, although there was some deposition of calcium in the blood vessels.

Courville states that the distribution and nature of these lesions, the recent ones of which resembled red softening in carbon monoxide asphyxia, suggest an anoxic origin. The patchy cell loss in the cortex and the absence of cerebral vascular disease are in agreement with this possibility.

MANDEL, Philadelphia

HYPNOTIC PHENOMENA, INCLUDING HYPNOTICALLY ACTIVATED SEIZURES, STUDIED WITH THE ELECTROENCEPHALOGRAM. B. E. SCHWARZ, R. G. BICKFORD, and W. C. RASMUSSEN, *J. Nerv. & Ment. Dis.* 122:564 (Dec.) 1955.

Eleven physicians, and 35 patients suspected of suffering from seizures, served as subjects of the investigation to ascertain the effect of hypnosis on the EEG. Although the EEG was unaltered when the subjects with their eyes closed imagined a scene, when hypnotic visions were experienced, alpha activity was suppressed in nine subjects and five had lambda waves. These effects were unaltered by *d*-lysergic acid. There was no difference in the effect of multiple pinpricks upon the EEG when the subjects were in the waking state or in a state of hypnotic analgesia. Also, movement of a hypnotically induced phantom limb, cataplexy, and regression did not alter the EEG. Hypnotically induced sleep induced changes comparable to those of natural sleep. In 10 subjects suspected of seizures but having normal EEG tracings, hypnotic suggestions reproduced their seizures, which were also terminated by hypnotic suggestions. The EEG was unaltered by these suggestions.

BERLIN, New York.

"VOODOO" DEATH. W. B. CANNON, *Psychosom. Med.* 19:182 (May-June) 1957.

This is a reprint of an article published in 1942 in the *American Anthropologist* by Walter B. Cannon. In a review of the literature up to that time, Cannon convinces himself of the reality of the use of spells, sorcery, or black magic to produce death in widely scattered parts of the world. He cites examples from South Africa, New Zealand, and Australia. In Africa a young Negro unknowingly eats of the banned wild hen—a food strictly forbidden. Years later, when told of this, he becomes overcome by fear and dies within 24 hours. In North Queensland a doctor examines an obviously seriously ill and extremely weak native and finds no signs or symptoms of disease. He learns that his patient has had a hex placed on him by "having a bone pointed at him." This hex is placed by a witch doctor, and the patient is convinced that he will die. He is saved only at the last minute, when the white physician forces the witch doctor to retract his hex. Almost instantaneously the native regains his full physical strength.

Cannon then asks himself whether an ominous and persistent state of fear can end the life of a man. Through experiments with cats to observe rage and fear reactions, he feels that these emotions produce similar effects on the body. These are called the sympathetic or sympatheticoadrenal response. Prolonged emotional stimulus, he proposes, could result in a disastrous fall in blood pressure, resulting in inadequate circulation and, eventually, death. Low blood volume resulting from dehydration could further intensify this condition.

Cannon feels that such changes might be noted if one could examine such a hexed patient and find a thready pulse, cool moist skin, and rapid respiration, and if the patient could be subjected to laboratory test and evaluated as to hemoconcentration, blood pressure, and blood sugar. He concludes by stating that he hopes the observer will conduct at least the simpler tests before the victim's last gasp.

AIGNER, Rochester, Minn.

ON THE PHENOMENON OF SUDDEN DEATH IN ANIMALS AND MAN. C. P. RICHTER, *Psychosom. Med.* 19:191 (May-June) 1957.

A review of Cannon's article on "Voodoo Death" is submitted by Richter, and further experimental work with animals is recorded in this connection.

The author measured the endurance of rats by means of swimming survival time, using glass cylinders with levels of water to prevent standing and jets of water from above to preclude floating. The end-point (drowning varied greatly from 10 or 15 minutes to 81 hours.

Through measurement of the heart rate by means of electrocardiograms, the records indicated that the rats succumbing promptly died with a slowing of the heart rate rather than acceleration. The hearts were also shown to have stopped in diastole, distended with blood. Slowing of respiration and drop of body temperature were also noted. These findings indicate a vagus death, which is the result of overstimulation of the parasympathetic, rather than the sympathetic, system.

Applying this to the understanding of "voodoo death," as postulated by Cannon, which the latter felt to be primarily a sympathetic change, Richter feels that the victim is not set for fight or flight but, rather, seems resigned to his hopeless fate.

AIGNER, Rochester, Minn.

EXPERIMENTAL GASTRODUODENAL LESIONS INDUCED BY STIMULATION OF THE BRAIN. J. D. FRENCH, R. W. PORTER, E. B. CAVANAUGH, and R. L. LONGMIRE, *Psychosom. Med.* 19:209 (May-June) 1957.

Bipolar electrodes implanted stereotaxically in the hypothalamic areas of 60 monkeys were stimulated four times each day with 5 to 8 volts. Of the 60 monkeys, 19 were felt to be given adequate stimulation and form the basis of this report. Eight of the animals were found to have significant lesions of the upper alimentary tract—three had focal pyloric lesions, three focal lesions in the first part of the duodenum, and two diffuse stomach and duodenal changes.

All animals in the test group which developed gastroduodenal lesions received excitation currents to a low midline axis in the hypothalamus. The remaining 11, in which visceral changes did not occur, had received stimulation outside this central hypothalamic region.

The possibility of these findings relating to the clinical "psychosomatic" disorder of peptic ulcerations is discussed.

AIGNER, Rochester, Minn.

ABSTRACTS FROM CURRENT LITERATURE

PSYCHOANALYTICAL OBSERVATIONS IN TWO CASES OF THROMBOPHLEBITIS MIGRANS. J. A. P. MILLET and J. F. DYDE, *Psychosom. Med.* 19:275 (July-Aug.) 1957.

Millet and Dyde report two cases of recurrent idiopathic thrombophlebitis treated with long-term psychotherapy.

Both patients were men in their 30's who had made unsuitable marriages. Despite manifest differences in religious, social, and racial backgrounds, it was felt there was a similarity in their strong affectionate ties to their parents. Their fathers were both passive in establishing family discipline; their mothers were dominant. Although strongly attached to the mother, they sought to escape by marrying women whom their mothers considered unsuitable.

The authors postulate the thesis that periods of extreme anxiety "led to the sudden and explosive discharge over the autonomic nervous system, with disturbances in the humoral regulatory system; the consequent changes in the vascular tree and blood composition leading to the thrombotic end result." In both cases improvement of the peripheral vascular disturbances coincided with the period during which intensive psychotherapy was introduced into the therapeutic program.

AIGNER, Rochester, Minn.

DENIAL MECHANISMS IN MASKED EPILEPSY. D. L. TIPPETT and I. PINE, *Psychosom. Med.* 19:326 (July-Aug.) 1957.

On the basis of the review of the clinical history of nine patients, Tippet and Pine present a concept of "masked epilepsy." The patients were unrecognized epileptics under treatment for various psychiatric symptoms. They presented a multiplicity of psychiatric conditions—four had hysterical reactions, two schizoid personalities, one a depressive reaction, another an obsessive-compulsive psychosis, and the last, an adolescent personality. All presented symptoms which were so stressed that the diagnosis of epilepsy was masked and not determined until the EEG evidence was available.

In the authors' opinion, the masking results from denial mechanisms produced by unconscious motivation. These patients differ from the epileptics who avoid detection of seizures on a conscious level by concealment or lying. All the patients functioned in such a way as to deny their epilepsy and were unaware of doing so.

Although antiepileptic medication was used, the fundamental approach was psychotherapeutic and emphasized acceptance and support of the patient with epilepsy.

AIGNER, Rochester, Minn.

Meninges and Blood Vessels

CAUSE OF DEATH IN RUPTURED INTRACRANIAL ANEURYSMS. J. BEHIN and R. D. CURRIER, *A. M. A. Arch. Int. Med.* 99:771 (May) 1957.

Behin and Currier review a series of 51 autopsy cases of intracranial aneurysm; of these, 45 cases presented a ruptured aneurysm, and in 10 of this number death was probably from causes not directly related to the ruptured aneurysm (for example, demonstrated associated cerebral infarctions). The 35 remaining cases (20 of men and 15 of women) were studied in some detail and could be divided into three groups. In 40% of them the anterior cerebral or anterior communicating vessels were involved; in 35% the supraclinoid portion of the internal carotid and middle cerebral arteries, and in the remaining 25% the posterior portion of the circle of Willis. Of these three groups, only the second (involving the carotid and middle cerebral vessels) showed clearly defined lateralizing signs, usually a hemiplegia. Patients with lesions of the anterior cerebral and communicating vessels frequently evidenced bilateral pyramidal findings, whereas those having aneurysms of the posterior portion of the circle frequently underwent sudden unconsciousness and rapid death, without any features suggesting their posterior fossa location. Aneurysms in the anterior location tended to rupture into one or both frontal lobes, as well as into the lateral ventricles. The second group of aneurysms tended to bleed into the temporal lobe and lateral ventricles, whereas the posterior lesions tended to rupture into the third and fourth ventricles, cerebellum, and adjacent portions of the neuraxis. Intraventricular bleeding was present in 32 cases, of which 26 showed associated intracerebral hemorrhage. There were two cases of subdural hemorrhage. Close correlation between the amount of bleeding and the rapidity of death was evident in most cases of intraventricular hemorrhage, exclusive of third-ventricle involvement. Patients with blood-distended ventricles usually died within 48 hours, whereas all patients living over six

days following the ictus showed little or no blood in the ventricles. Subarachnoid hemorrhage was present in all cases, and the amount of subarachnoid bleeding did not appear to be a significant factor in determining the outcome. In several instances a lumbar puncture was succeeded an hour or so later by rapid worsening and death, and cautious and frugal use of the spinal tap in all instances of subarachnoid hemorrhage is advisable.

PARSONS, Montrose, N. Y.

SUBARACHNOID HEMATOMA COMPLICATING RUPTURED INTRACRANIAL ARTERIAL ANEURYSM.

M. B. BORNSTEIN and M. B. BENDER, A. M. A. Arch. Int. Med. 100:50 (July) 1957.

Bornstein and Bender analyzed the autopsy findings in a group of 20 patients with ruptured intracranial aneurysms. In nine cases there was blood in the subdural space, with large subdural hematomas present in five instances. Review of the case summaries failed to disclose specific clinical findings which would have enabled differentiation of the cases with subdural hemorrhage from those with subarachnoid and intracerebral bleeding alone. The site of the aneurysm was not a factor in determining the incidence of subdural bleeding. In only two cases of the autopsied group would evacuation of the subdural hematoma have materially altered the outcome, although the authors describe a favorable course in two additional patients with ruptured intracranial aneurysms in whom surgical exploration disclosed substantial subdural hematomas, which were subsequently evacuated. Subdural hematomas may be trivial, massive, and rapid, or large and slowly progressive. It is the latter type in which surgical intervention may prove life-saving. In the absence of a characteristic syndrome, attention should be drawn to the possibility of subdural hematoma in a patient with suspected ruptured intracranial aneurysm who develops gradual obtundation of consciousness and focal neurologic signs. Conversely, the possibility of ruptured aneurysm should be considered in all cases of suspected subdural hematoma, as the former is the second most frequent cause of subdural hematoma, being responsible for about 8% of cases.

PARSONS, Montrose, N. Y.

THROMBOSIS OF THE INTERNAL CAROTID ARTERY IN THE NECK. S. RESNIKOFF S., J. CÁRDENAS Y C., and P. LOEWE, A. M. A. Arch. Int. Med. 100:453 (Sept.) 1957.

The authors report three cases of spontaneous thrombosis of the cervical portion of the internal carotid artery. Only one patient developed unilateral amaurosis, which was transitory. The importance of the Sanchez-Perez method of serial angiography in achieving a diagnosis is stressed, and angiographic study of the intact side is mentioned, only to be rejected for its inherent hazards. In their review of the subject, the authors mention the variability of course, which is to be correlated with the functional integrity of the circle of Willis and other vessels, and the element of spasm, as well as recanalization of thrombi in certain cases. The preferred surgical treatment consists of internal carotid-external carotid anastomosis or resection of the thrombosed segment with subsequent arterial graft reconstruction. In the event that chronic inflammatory changes have resulted in formation of adhesions between the internal carotid and the lateral process of the axis (producing chronic carotid compression, leading to the intimal damage and thrombosis), a decompression of the vessel by lysis of the adhesions and resection of the lateral process should be performed.

PARSONS, Montrose, N. Y.

SPONTANEOUS FRACTURES IN TUBERCULOUS MENINGITIS. C. CHOREMIS, C. PAPADATOS, A. ARZIMANOGLU, and C. DROSOS, A. M. A. J. Dis. Child. 94:17 (July) 1957.

Four infants with tuberculous meningitis presented spontaneous fractures during the course of their hospitalization. All were treated extensively with streptomycin, and two with isoniazid and cortisone in addition. Determinations of calcium and phosphorus were normal. Immobilization was not complete, but because of age they walked little. The fractures were all in the lower limbs, and x-rays revealed osteoporosis but no evidence of osteomyelitis. Immobilization of the affected member with a cast was used, and callus formation was generous.

The authors postulated that in the course of tuberculous meningitis the hypothalamus is involved either by the toxic action of streptomycin or by involvement of the diencephalon in the meningitic process. They suggest caution in the use of cortisone because it enhances osteoporosis.

SIEKERT, Rochester, Minn.

ABSTRACTS FROM CURRENT LITERATURE

SPINAL FLUID ALCOHOL IN YEAST MENINGITIS. R. TYLER, *Am. J. M. Sc.* 232:560 (Nov.) 1956.

Although yeast and bacterial meningitides reduce the concentration of spinal fluid sugar, it was postulated that their respective products of glucose metabolism might be different and the difference could serve to distinguish between the two types of infection. It was found that in three cases of cryptococcal meningitis there was a positive test for alcohol but in bacterial meningitis the test for alcohol was negative despite reduced cerebral spinal fluid sugar in both infections. The only false-positive test occurred after the patient had ingested a large amount of alcohol.

BERLIN, New York.

TRIGEMINAL NEURALGIA AND ARTERIOVENOUS ANEURYSM OF THE CEREBELLOPONTINE ANGLE. A. B. EISENBREY and W. M. HEGARTY, *J. Neurosurg.* 13:647 (Nov.) 1956.

Trigeminal neuralgia is a rare occurrence in children. Eisenbrey and Hegarty report a case of trigeminal neuralgia in a 12-year-old child which occurred secondary to a large arteriovenous malformation of the right cerebellopontine angle, producing severe face pain, pronounced cerebellar dysfunction, and mental deterioration.

MANDEL, Philadelphia

OPHTHALMIC ARTERY ANEURYSM. R. R. GOLDIN and M. L. SILVER, *Radiology* 68:727 (May) 1957.

Goldin and Silver report the case of a 50-year-old woman who had suffered progressive loss of vision in the left eye for three months. At the time of admission to the hospital the patient could detect only shape and movement with the left eye. There was nasal hemianopsia on the left. The temporal portion of the left optic disk showed marked pallor, but the nasal portion showed normal coloration. No pulsation or bruits could be heard over the skull or eyeballs. Routine skull films showed nothing abnormal. However, studies of both optic foramina showed an area of bone erosion adjacent to the lateral side of the left optic foramen. The right optic foramen appeared normal.

Left carotid angiography was performed, which showed a large aneurysm of the left ophthalmic artery. The aneurysm was approached surgically through the roof of the left orbit, but the ophthalmic artery could not be ligated, since the aneurysm arose either from or extremely close to the left internal carotid artery. Two days later the left internal carotid artery was ligated, and the patient began to be able to detect light with the left eye.

It was believed, in retrospect, that the diagnosis could have been made before the cerebral angiogram was performed. The clinical symptoms and signs combined with the finding of bone erosion on the lateral side of the optic foramen made aneurysm of the ophthalmic artery a reasonable probability, despite the fact that such a lesion is rare.

WELAND, Grove City, Pa.

Books

BOOK REVIEWS

Modern Trends in Neurology. Second Series, edited by Denis Williams. Price, \$13.50. Pp. 374. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Bros.), 49 E. 33d St., New York 16, 1957.

This second volume, entitled "Modern Trends in Neurology," contains twenty-four essays by twenty-three authors, twenty of whom are British, discussing varied topics in which neurologists are evincing investigative interest currently. No attempt has been made to cover all aspects of present-day neurological development. The orientation of the volume is toward the basic sciences, and ten of its chapters are specifically concerned with anatomy, biochemistry, physiology, and pathology. An index of current neurological emphasis is provided by the inclusion of four chapters dealing with cerebrovascular disease, three concerning muscle disease, three discussing various aspects of epilepsy, and two concerning disorders of the base of the skull and the cervical cord. In addition are included papers on tissue reaction in the nervous system, acute viral encephalomyelitis, aural vertigo, sarcoidosis of the nervous system, and neurosurgical treatment of disorders of the affect.

The editor instructed the contributors "to assume a high level of knowledge in his readers, to review current work critically and concisely, and to follow the trend of his work as far into the future as scientific propriety will allow." In carrying out these instructions, the authors have succeeded admirably.

In a collection of such consistently high quality, it is difficult to select the most outstanding contributions, but certainly deserving of special praise are the two chapters by C. E. Lumsden on the chemistry of the myelin and sheath cell and on cell structure and physiology in relation to myelin; that by Valentine Logue on cervical spondylosis, and that by Donald B. Tower on the medical treatment of seizures. The writers do assume a high level of knowledge, and thus the book is not for the novice; it should, however, provide for the thoughtful student a wealth of information about the present status of our knowledge and guidance for speculation about developments of the future.

CHARLES E. WELLS, M.D.



a salute to
medical school progress

MEDICAL EDUCATION
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SECTION ON PSYCHIATRY

Classification and Rating of Emotional Experiences

Special Reference to Reliability of Observation

DAVID A. HAMBURG, M.D.; MELVIN A. SABSHIN, M.D.; FRANCIS A. BOARD, M.D.;
ROY R. GRINKER, M.D.; SHELDON J. KORCHIN, Ph.D.; HAROLD BASOWITZ, Ph.D.; HELEN HEATH, Ph.D.,
and HAROLD PERSKY, Ph.D., Chicago

I

A central task of psychosomatic research lies in the working out of relations between psychological and physiological processes by means of systematic, empirical inquiry, using the best available procedures for all processes under scrutiny. Although many difficulties hindering physiological studies in intact humans require analysis and solution, the present paper represents an attempt to identify several of the major methodological problems on the psychological side and to report on efforts made to cope with them.

Among the main difficulties apparent in published psychosomatic research have been the following: (1) skimpy, impressionistic observations of behavior with meager speci-

fication of psychological processes; (2) absence of checks to determine whether similar results could be obtained if the observations were made again under essentially the same conditions, or if another observer viewing the same phenomena could obtain the same results, and (3) lack of quantitative estimates for the psychological variables, thus sharply limiting the kinds of comparisons that can be made between them and the physiological variables.

In the present research we have taken several steps designed to lessen these difficulties, though we are well aware of their complexity and the need for many further efforts in this direction. In an effort to obtain adequate psychological data, we arranged for two nonparticipant psychiatric observers to view and listen to the entire four days of experimentation, including two affect-evaluation interviews conducted by another psychiatrist each day. In addition, we attempted to specify the criteria for each affect as clearly as the phenomena would permit. In order to facilitate systematic comparison of the psychological data with the readily quantifiable physiological data, we developed a rating scale for anxiety, anger, and depression. These rating scales were constructed to facilitate comparisons of the affects with each other, as well as with nonaffective variables, and were designed to make explicit the sort of quantification which

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This study was carried out as part of a program of research into the psychosomatic organization of anxiety and supported by the U. S. Army under Contract No. DA-49-007-MD-469 through the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, and by the State of Illinois Mental Health Fund.

is common and useful in clinical work. Finally, we undertook several analyses of the affect ratings in order to determine the extent to which two observers can agree independently when exposed to the same data, and the conditions which facilitate such agreement.

II

Various members of our research group have been investigating psychological stress responses since World War II.¹ Some of our studies have included the use of patients with anxiety neuroses,² anxiety-prone subjects,³ and subjects in a stressful life situation.⁴ In all our work we have been concerned with the establishment of quantitative rating scales in order to compare changes in emotional behavior with changes in various somatic functions. In our paratrooper studies⁴ we found reliability in the analyses of subjects' anxiety by the same rater repeated after several months, and good reliability between two raters and between ratings determined by observers and quantitative estimates of anxiety by the subjects themselves.

As our experience in stress research increased, we became increasingly interested in further differentiation within the psychosomatic network of emotions. It might be, for example, that anxiety is more closely related to epinephrine secretion than is anger, whereas anger is more closely related to non-epinephrine secretion than is anxiety. In order to clarify such psychosomatic relations, it is necessary to measure each subsystem in its own right by criteria defined independently of the others. Thus, emotions are defined not by physiological or biochemical criteria but by verbal and non-verbal behavior indicative of psychological states for which comparatively little inference is required.

If we are able to show that two or more people can independently agree regarding the kind and degree of affect present, and also find high agreement on the direction and extent of change resulting from oc-

casions of stressful stimuli, and, finally, show that the quantitative ratings fit with the measurements of level and change in other portions of the psychosomatic system (independently measured), we have gone a long way toward establishing construct validity for the affects.^{5,6}

In a statement preliminary to the report of a series of experiments on anxiety covering several years,⁷ we have considered the general concept of anxiety as the principal function of a system of psychosomatic organization composed of many subsystems. We chose to focus our attention on four of these: anxiety as a subjective reportable experience; the visual perceptive system; the endocrine system, and the autonomic nervous system. Naturally, we could utilize only a fragment of the total functioning of each of the last three systems for measurement in a complicated multidisciplinary research striving for simultaneity of observations. Nevertheless, we attempted to study functions of biological importance that could be measured reliably.

III

The experimental procedure designed to test the relationship of anxiety, anger, and depression with several somatic systems consists of four days of testing for three hours each. The first day is preexperimental, in which the subject is tested as he becomes acclimated to the experimental setting and test procedures. The three subsequent experimental days consist of periods before, during, and after (pre, during, and post) an experimental intervention of a stress stimulus. Thus it is possible to compare the amount of change in each variable separately and jointly as a function of an inducing stimulus.

In order to minimize the errors of participant-observers' involvement with the subject resulting in difficulty in maintaining objectivity or inducing desired responses, we utilize two nonparticipant observers. They observe the subjects through a one-way vision mirror from an observation

room, in which they can also hear everything that goes on in the experimental room. The observers keep detailed behavioral notes on the entire procedure as independently as possible.

The patient communicates both verbally and nonverbally that he is probably experiencing emotional arousal and distress of a certain type. The observers have a continuous flow of information from the patient as they watch him go through the entire experimental procedure, several hours each day. When he is alone, they notice his facial expression, his movements, and the remarks that he mutters to himself. When experimenters enter the room, the observers note the patient's initial reaction to them, his verbal exchanges with them, and his behavior in the course of each procedure. Thus a large amount of data over a considerable time span has a bearing on the estimation of anxiety, anger, and depression.

However, these cues are often inconclusive. They may suggest, for example, that the patient is suffering and yet not provide sufficient specifications as to the nature of his suffering. Sometimes, the patient's behavior when alone (for example, repeated grimacing) may alert the observers to the fact that something important is occurring psychologically, yet leave them wondering about its specific content. For these reasons, we utilize two interviews by a psychiatrist for the purpose of eliciting the affects. The first is conducted at the end of the pre period, just before the stress interview, and the second at the end of the morning, making it possible to review all the developments of the day's experiment. These evaluation interviews systematically inquire into the presence, manifestation, and degree of anxiety, anger, and depression. Furthermore, questions raised by observations earlier in the morning can then be specifically explored by the interviewer in an effort to clarify vague or doubtful points. Thus, the observers have available extensive verbal reports by the patient of his emotional state at various points throughout the morning

and an opportunity to compare the overt communication with the introspective description of the patient's feeling state.

The nonverbal communications of emotional experience refer primarily to behavior on the part of the patient which the observers have in the past associated with a certain kind and/or intensity of emotional experience—both in themselves and in others. They may alert the observers to aspects of the patient's experience which might otherwise be overlooked—if, for example, the observers were using a verbatim transcript. Similarly, the nonverbal communications help in deciding whether the subject is exaggerating or minimizing a given kind of emotional experience in his verbal report. Sometimes the patient reports a disturbance of much greater intensity than observation suggests. This is particularly true of the experienced patient who has been in treatment with various psychiatrists and who feels that the patient role calls for dramatic emotional performance for someone's benefit. On the other hand, patients sometimes appear to be suffering much more than they are willing or able to admit, especially if they consider emotional expression as a sign of weakness. Thus, the opportunity for rather prolonged, detailed observation affords the possibility for refining and qualifying in the estimate of the patient's emotional state.

Each of the three terms—*anxiety*, *anger*, and *depression*—is a generic term referring to a class of phenomena containing within it a "family" of feeling states which share a common mode of experience, but differ in intensity. Thus, there are a series of synonyms for anxiety, anger, and depression which can be ordered as different degrees of intensity along a single dimension. In common usage, these terms are not sharply defined and overlap considerably; yet they gradually shade from a low to a high order of intensity while preserving a common core of experience which is identifiable by the "family" name. We have therefore arranged a series of such synonyms, beginning

with those usually referring to low- and moving gradually toward high-order intensity. 1. Anxiety: apprehension, foreboding, danger, dread, panic. 2. Anger: annoyance, irritation, resentment, antagonism, hostility, rage, fury. 3. Depression: sadness, regret, discouragement, dejection, gloom, despondency, despair.

IV

In an effort to make the three affect scales as comparable as possible, general statements of intensity were employed to define points along the scale. By virtue of their generality, the same statements could be used on all three affect scales: 0, particular feeling absent; 1, distinct but not impressive; 2, impressive; 3, intense; 4, unusually intense; 5, extremely intense; 6, most extreme ever reported. At the outset, the investigators believed it would be sufficient to use a seven-point scale for each affect, ranging from 0 to 6, as outlined above. However, when the experiment actually began, the psychiatric observers felt it necessary and possible to make finer distinctions. Thus, in the pilot studies the observers agreed upon the need for adding plus and minus signs between each of the points already identified on the scale. This, in effect, converted the 7-point scale into a 19-point scale and functionally changed the numerical designations as follows: 0, feeling absent; 3, distinct but not impressive; 6, impressive; 9, intense; 12, unusually intense; 15, extremely intense, and, 18, of most extreme intensity ever reported.

The scales employed in this study are relative: On any given scale 2 is more than 1 and less than 3; but the distances between points may not be equal and the points are certainly not precise. A change in direction is probably meaningful, especially if it is large. In other words, if a person's anxiety rating changes from 1 to 2 in the course of the morning, it is very likely that his anxiety has actually increased, but we cannot specify exactly how much it has increased, nor do we imply that he is twice as anxious as he

was before. Although the intervals between the points on the rating scale are not necessarily equal, therefore suggesting use of nonparametric statistical methods, we found it useful to treat the intervals as if they were equal and employ parametric methods. It is fruitful to assume a rough equality between intervals and see what empirical consequences flow from such an assumption, even though we know such equality cannot be precise.

The scales for the individual emotions are intended to be at best roughly equivalent; the actual values on each are derived comparatively. The highest rating was given to the affect which, in the total context of this patient's behavior during the time of observation, was considered most prominent. Frequently, the observers would see some evidence of all three affects during a particular time period; yet they might feel that anger, for example, was more prominent than anxiety or depression, taking all of the patient's behavior during the specified time span into account, and so anger would be rated higher than the other two.

On the initial day (preexperimental day) the ratings were made primarily from the frame of reference of other patients; that is, an attempt was made to compare this particular subject's behavior with those of other subjects and to place him as accurately as possible in the subject population. After the preexperimental day, during the three subsequent experimental days, the ratings were no longer made primarily within an inpatient frame of reference, but were made largely on an inpatient basis. The observers asked themselves: "Is this subject more or less anxious than he was yesterday, and how much?" Thus, the observers attempted to get a subject's ratings anchored correctly within the group at the outset, and thereafter tried primarily to keep his own ratings consistent with each other.

Each rating for a given period (pre, during, and post) covered a considerable time span, ranging from a half-hour to an hour, so that it was often necessary for the observers

to average the fluctuations in arriving at a rating for a given period. For example, the patient might show rather extreme disturbance for five minutes, after which his disturbance would ease considerably. At the peak, his emotional intensity would call for a high rating, while during most of the period his emotional intensity would call for a lower rating. The result would be an intermediate rating. Fortunately, the fluctuations within a given period were usually less extreme than this example, but occasionally they were quite striking. The averaging process was based on a complex judgment of the total situation.

The two psychiatric observers made a deliberate, consistent effort to avoid communication about the patient's behavior while an experiment was in progress. It was possible to avoid completely any mention of numerical estimates. At the end of each morning, each observer reviewed his notes independently of the other observer and recorded his rating for anxiety, anger, and depression. Only when these ratings had been independently recorded were they discussed. Then each rater tried to cite the evidence on which his ratings were based and attempted to correct the other's errors. If the two ratings were not exactly the same, the final rating was decided after a thorough discussion of the differences between them, and a final consensus was achieved.

We present here an analysis of the two observers' ratings to determine their agreements and disagreements which could give some indication as to the reliability of the rating scale if used again with the same definitions and with the same methods. Our analysis for the purposes of this report is undertaken on two groups of subjects (A and B) utilized for various types of stress research.

V

1. *What is the extent of agreement and disagreement between the psychiatric observers?*

In answering this question, the expanded 19-point scale is utilized and the affect

ratings of anxiety, anger, and depression are considered. More than 70% of the paired ratings for each affect in Group A fall within one rating unit of each other. This implies that on over 70% of the occasions when one of the observers rated an affect at a particular level—for example, 6—the other observer rated it at either 5, 6, or 7. On 95% of all occasions the raters are within ± 3 units of each other on the 19-point scale. To illustrate numerically, a value of 6 by one rater would fall in the interval of 3 to 9 inclusive by the other rater on 95% of the occasions. The maximum obtained difference is 6 points, and its single occurrence is in the rating of anger. The greatest number of exact agreements is found for depression; however, this is only slightly higher than the agreements for anger and anxiety. On approximately 33% of all occasions of ratings the observers exactly agree with each other. Although the above-mentioned figures definitely apply to Group A, the findings are maintained on the smaller (second) group (B). In this latter group, the only instance in which the raters are more than 3 units apart occurs in rating of anxiety, and the difference is 4 units. The extent of difference between observers for Group B is slightly less than that found for Group A, and there are relatively more occasions when there is exact agreement.

2. *How do the raters correlate on their estimation of all affects?*

Since a difference in ratings could be due either to a difference in means or to a difference in pattern between the raters, statistical procedures for estimating both of these have been utilized. Three Pearson r 's—one for each affect—were computed for every subject across occasions to determine the degree of similarity between patterns. In order to obtain an over-all assessment of this relation, all the r 's were converted to z 's, and the mean z for each affect was computed and reconverted into an r (Table 1). Since the P value for each r on both Group A and Group B subjects is far beyond the 0.001 level, the results indicate great similarity in patterns between the raters.

TABLE 1.—Pearson Correlations Between Raters

	Group A (N=11)			Group B (N=4)		
	Mean <i>r</i>	<i>df</i> *	<i>P</i>	Mean <i>r</i>	<i>df</i>	<i>P</i>
Anxiety	0.78	70	<0.001	0.82	19	<0.001
Anger	0.87	70	<0.001	0.81	19	<0.001
Depression	0.81	70	<0.001	0.85	19	<0.001

* The degrees of freedom were determined by adding the *df*'s for each correlation and then subtracting 1 for the computation of the mean.

3. What is the extent of agreement on the mean affect ratings?

In contrast to the previously discussed analysis, which involved the question of whether or not the two sets of ratings parallel each other throughout the entire experiment, this analysis compares the overall means of the ratings. When these values are subjected to *t*-test (Table 2), no significant differences between the raters regarding the affect means are obtained on Group A. The closeness between the two sets of means which is evident by inspection is confirmed by analysis. However, on Group B the tendency for Rater A to rate higher on anxiety reaches the 0.10 level, and the reverse tendency on depression reaches the 0.05 level.

4. Do the raters agree upon which of the three affects being estimated is predominant for a given period?

The purpose of this analysis is to determine whether consensus can be obtained regarding which aspect of the patient's emotional behavior is most prominent during a specified period of time. A χ^2 -analysis is computed on the frequency of agreements of the predominant affect.

The following rules were established for tabulations.

The result is called an agreement when both raters estimate one affect as higher than either of the other two. If both tie on the two highest affects and rate the third as lower, this result is also accepted as an agreement. All other patterns are termed disagreement, indicating the stringency of the standards. For example, by these criteria, if one observer makes a rating of 3

for anger, anxiety, and depression while the other rates anger and depression as 3 and anxiety as 4, this pattern is termed a disagreement.

Analyses are carried out for both Group A and Group B. Of 11 subjects in Group A, 5 were observed by both raters during all their occasions, whereas there were a few occasions for the remaining 6 at which only one of the observers were present. These two subgroups are analyzed separately as well as combined. Since the raters had three choices for the predominant affect, the expected agreement would be one-third of all occasions. As Table 3 illustrates, the obtained agreements for the total of 93 occasions in Group A number 54, while the disagreements number 39. χ^2 indicates a *P*-level of <0.001. A comparable probability level is obtained by the analysis for the five subjects with complete ratings. However, on the remaining six subjects—those with incomplete ratings—the χ^2 is at approximately the 0.10 level. On this group there were 20 agreements and 23 disagreements. These findings suggest that when both observers rate on every occasion, they improve in their ability to discriminate the predominant affect. On Group B, the same χ^2 -analysis yields a significance level of <0.001, as is recorded in Table 3. The obtained frequencies are 20 agreements and 8 disagreements, while the expected frequency rate is approximately the reverse. This is approximately the same extent of agreement of predominant affect that is obtained on the five Group A subjects on whom there are complete ratings.

TABLE 2.—Comparison of Means of Raters

	Group A (N=11) Number of Ratings = 93			Group B (N=4) Number of Ratings = 28		
	Rater A	Rater B	<i>D</i>	Rater A	Rater B	<i>D</i>
Anxiety	3.60	3.39	0.21	4.28	3.97	0.31*
Anger	3.40	3.44	-0.04	3.82	3.73	0.09
Depression	2.76	3.07	-0.31	3.45	3.98	-0.50†

* *P* < 0.10.

† *P* < 0.05.

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TABLE 3.— χ^2 Analysis Comparing Two Raters' Judgments of Highest Affect on Each Occasion

	Group A						Group B	
	Complete Ratings (N=5)		Partial Ratings (N=6)		Total (N=11)		Total (N=4)	
	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree
Obtained	34	16	20	23	54	39	20	8
Expected	16.7	33.3	14.3	28.7	31	62	9.3	18.7
	$\chi^2=25.38$		$\chi^2=2.73$		$\chi^2=24.50$		$\chi^2=16.75$	
	$P<0.001$		$P<0.10$		$P<0.001$		$P<0.001$	

5. Do the observers agree on direction of change in a particular affect from period to period?

When the observers established their consensus ratings, they noted a marked tendency of agreement in regard to rating quantitative change of a particular affect from one period to the next period. For example, if one observer rated the patient as becoming more anxious in the during period than he had been in the pre period, we may ask whether the other rater tended to agree with this direction of change. For Group A this relation was investigated by means of a $3 \times 3 \chi^2$ for each variable. Entries in Table 4 indicate whether or not the raters agreed in judging that the affect increased, remained the same, or decreased. Agreement on all variables was far better than the 0.001 level of significance. Since the number of occasions for Group B was too small to warrant a comparable χ^2 , all ratings which indicated no change in affect for either or both raters were omitted. The extent of agreement on increases and decreases was evaluated by computing exact probabilities.

The probability level for anger is approximately 0.02; however, agreement on direction of change for both anxiety and depression greatly exceeds the 0.001 level. A summary of the data and the statistical evaluations are presented in Table 4.

6. Do the consensus ratings agree more closely with the findings in other systems measured than do the original individual ratings?

This question differs in purpose from the previous ones in that an external criterion serves as an estimate of the usefulness of the individual versus the consensus ratings. Since it had been found that there was a significant relationship between change in the consensus anxiety rating during each experimental day and change in 17-hydroxycorticosterone found in the plasma for comparable periods (Table 5), the same analysis was carried out with each of the individual ratings substituted for the final consensus rating. On the day of the greatest anxiety change, the 17-hydroxycorticosterone level showed the greatest tendency to remain elevated during the morning, whereas on the day of least anxiety change the 17-hydroxycorticosterone showed the least tendency to remain elevated. When the individual ratings were substituted for the consensus ratings, the results based on one of the raters were about equal to the consensus ratings; however higher significance was obtained from the other set of ratings. Comparable analysis was made with the combined affect ratings, and in this situation, when more data were involved, the relation-

TABLE 4.—Comparison of Direction of Change Scores Between Raters

Anxiety				Anger Group A				Depression			
	Up	Same	Down		Up	Same	Down		Up	Same	Down
U	29	6	2	U	24	4	2	U	24	2	2
S	1	7	3	S	3	6	5	S	6	8	5
D	2	8	22	D	4	5	27	D	2	4	27
$\chi^2=42.58$				$\chi^2=45.03$				$\chi^2=54.93$			
$P<0.001$				$P<0.001$				$P<0.001$			
Group B											
	Up	Down		Up	Down		Up	Down			
U	5	1	U	3	0	U	6	1			
D	0	13	D	1	10	D	0	13			
Exact probability $P<0.001$			$P=0.02$			$P<0.001$					

TABLE 5.—Comparison of Results of Analysis of Variance between Linear Component of Plasma 17-Hydroxycortisone When Occasions Were Selected by Consensus and by Each Rater Separately

Variable for selection of days	Group A Only					
	Rater A		Rater B		Consensus	
	F	P	F	P	F	P
Anxiety	13.33	<0.001	6.16	<0.025	6.19	<0.025
Combined affects	5.42	<0.05	6.91	<0.025	8.00	<0.01

ship emerged more strongly for the consensus than for either of the individual raters.

In summary, the raters show a high level of agreement on their rating of affect. They correlate highly on rating affects over all occasions, agree on which affect is predominant at any occasion, and agree very strongly on change in direction of affect, and also quite well on level of affect. The results indicate that two psychiatric observers are able to identify and classify emotional phenomena with considerable agreement in spite of the complexity, ambiguity, and transitory nature of these phenomena. While one may argue about the meaning of the phenomena, their presence and extent can be reliably estimated. In view of the fact that these ratings are also used to make comparisons with other systems being measured, the importance of the superiority of consensus ratings over individual ratings is an additional finding that supports the use of multiple observers in an experiment of this kind.

VI

In view of the extreme scarcity of reliability studies in the psychiatric and psychosomatic literature, we have paid considerable attention to the issue of agreement and disagreement between raters. One of the principal questions in this study is whether emotional phenomena are sufficiently definite to permit reliable identification and quantification by different observers. When we find that agreement between observers usually occurs (interobserver reliability)

and that a given observer, when exposed to the same data on two different occasions quite far apart in time, comes to the same conclusion each time (intraobserver reliability), we may assume some legitimate confidence in the method of observation. We then know that, within certain limits, a given set of data will lead to the same conclusion each time it is presented to an observer. Then, if two different sets of data are given different ratings, we are in a better position to decide whether the difference in ratings is due to an actual difference in the phenomenon under study or to an error in the method of observation. This point becomes crucial if we are particularly interested in distinguishing between subtle differences.

Although research on the reliability of psychiatric observation is rare, there are a few studies of special interest. For example, the study of Hunt, Wittson, and Hunt^{8,9} shows striking evidence of unreliability in psychiatric diagnosis. There were strong indications that the reliability of psychiatric judgment was related to the specificity of judgment required; that is, the greater the specificity of judgment, the poorer the agreement among psychiatrists. There was, for instance, a fair degree of agreement on placing each subject within a general diagnostic category: psychosis, psychoneurosis, or personality disorder. However, within each of these general categories their agreement was quite poor; that is, they could not agree on the specific diagnosis.

Similarly, Raines and Rohrer¹⁰ obtained diagnostic judgments on almost 1000 naval officer candidates. They found many instances in which a psychiatrist had a preferred diagnostic category, related to his own personality. Furthermore, when different psychiatrists examined the same man, they frequently saw quite different personality traits in him and applied different diagnostic labels.

If reliability of observation is important in psychiatric research, we must ask: What are the conditions under which independent agreement is most likely to be achieved?

While this problem has had very little attention in the psychiatric literature, it has been taken more seriously in the related fields of psychology and sociology. Bruner and Tagiuri¹¹ have recently reviewed a large literature on the recognition of emotions and the judgment of personality characteristics. They have called attention to four major technical problems in the reliable observation of emotional and personality variables.

1. The nature of the discrimination required in an emotion-judging task. They point out that it is more difficult to distinguish one unpleasant emotional state from another unpleasant one than it is to distinguish love and disgust. The difficulty of the task is one important factor that determines the reliability of observation.

2. The nature of the identifying labels the judges are asked to use.

Subjects reach higher agreement in judging if they are allowed to use their own terminology and categories. There is no reason to assume that different individuals are equally inclined to utilize the same categories for ordering emotional expression.

3. Adequacy of information. This seems to be a particularly important point. The accuracy of judgment appears to be directly related to the amount of information given the observer.⁶ Each item of relevant information narrows the range of likely alternatives. In general, then, "the more information about the situation in which an emotion is being expressed, the more accurate and reliable are judgments of the emotions."

4. The problem of sampling emotional expressions. There is a great variability in the ways used by different subjects to express the same emotion. Indeed, there is even some variability in the ways in which a given subject expresses a given emotion at different times. Therefore, it is important to have a rather wide sampling of expressions for each subject, and for the population of subjects from which a given subject is drawn. Both for cross-cultural and intra-cultural reasons, it is quite unwise to assume

a stereotyped set of behavior as the required expression for a given emotion. The observers must, if they are to make reliable estimates, know a good deal about each subject and about the type of subject he represents.

In a similar review, Heynes and Lippitt¹² come to three main conclusions about conditions which influence the reliability of observation in studies of human behavior.

1. Degree of inference

The less inference required of observers, the higher the degree of agreement. With category or rating systems which require a good deal of inference, it is clear that the most reliable are those in which the dimensions are clearly defined and the cues to be used by the observers are specified.

2. Definition of the unit of observation

The reliability of some systems is low because of unclear definition of the unit. Even when the units to be rated or classified may be fairly clearly stated, the observers may nevertheless disagree as to unit boundaries in actual observing situations. It is obvious that the degree of agreement as to coding can only be appropriately assessed when there is agreement first as to what is to be coded.

3. Training of observers

With category or rating systems which require some inference, the degree of reliability attained is very much a function of the amount of training which observers have had. The thoroughly trained observer has become maximally familiar with the definitions of the categories or dimensions. He has gotten practice in designating the unit of observation. He has gained skill in adopting the frame of reference which the system demands, and has practiced his art in the situation in which the behavior takes place. His own private definitions have been eliminated or have come to be shared using the system. In short, virtually all the sources of unreliability have been dealt with in the training process.

Our own ratings indicated that discrimination was better when more information was available. Thus two observers agreed more frequently when both observed all the experimental sessions of a given subject than when one observer missed an occasional session. It was also our impression that interobserver agreement was favored by the following factors: thorough sharing of a frame of reference by the two observers; considerable specification of criteria for the affects and their various levels; extensive

experience in the rating situation, and abundant information on the variables being rated.

VII

While we have so far placed considerable emphasis on the significance of reliability, extreme conclusions should not be drawn. We are not suggesting that a variable be included in an investigation *only* if two observers can usually agree independently on its presence and its extent. It seems to us that investigators who follow this procedure may well discard variables of great importance. On the one side, as we have already indicated, there is real danger in ignoring reliability considerations altogether, as is so often the case in the psychiatric literature, since we may then be dealing with hazy, undefined, and highly personal concepts which do not lend themselves to repetition of research. On the other side, however, is the danger that we may overlook variables of great importance if we insist upon a high degree of agreement early in the research. Observers may have a significant grasp of an important phenomenon which they cannot fully define at the outset. The history of reliability studies shows that the highest agreements are reached when virtually no inference is required, but it is also true that those judgments which require the least inference are often trivial. Many important variables in research on human behavior will require a moderate degree of inference and, therefore, will give only moderately high reliability. If, in terms of general knowledge of the problem under study, there is strong reason to believe that a variable may be an important one, an attempt should be made to develop reliable measurements of it; and yet the variable need not be thrown away if this proves difficult to achieve.

High reliability of observations means that they can be public rather than private, and repeated by the same investigators, or by others operating under essentially the same conditions. This does not mean that the

correctness or validity of the measure is any greater than if a single person is capable of observing, rating, or predicting a given process, especially in the early phases of a research. It is, after all, the "fit" of a given variable or subsystem with other subsystems which determines the usefulness of the observational process, regardless of how many people are involved in making the observations. Thus, in our own field of inquiry, a good deal is known about diurnal variation in plasma hydrocortisone in healthy human subjects and its responses to physical and psychological stress agents.³ We were led, therefore, to compare a rational consensus of the two ratings of affect with an arithmetical average of the two ratings and with the ratings of each observer alone with respect to the closest correlation with plasma hydrocortisone. The consensus rating gave a closer relationship with the hormone variable than the individual ratings or their average.

We mention this chiefly to stimulate systematic, interobserver comparisons in psychosomatic research. There are several ways in which this might be useful, but discussion of these issues goes beyond the scope of the present study. Our specific finding on interobserver comparison suggests that the consensus method may facilitate accurate observation. In the first place, it extends the range of observation by bringing in two observers instead of one; and, in the second place, it provides for a final rating based upon the evidence of each observer, rather than an arbitrary averaging of their two ratings. There are some instances in which one rater is simply wrong and the other right; the difference does not necessarily lie somewhere between them. By requiring a consensus, each observer must produce the information upon which his rating is based, and the final rating goes to the solidier evidence. This has the additional advantage of building into the procedure a lever to pry more and more information out of the intuitive realm. By trying to provide the evidence upon which rating is based, and in the course of discussing the consensus rat-

ing, the observers become increasingly aware of the behavioral cues which serve as criteria for the rating. Thus the consensus has advantages on several counts, provided that the interpersonal conditions within the research group facilitate independent but co-operative relations among the observers.

Summary

Because of the importance of emotional responses in psychiatric and psychosomatic theory, a need arises for a systematic, explicit approach to their classification and rating. Can affects be dealt with reliably in studying human behavior, or are they so vague and difficult as to preclude one observer's repeating the observations of another? Is there any usefulness in quantifying emotional responses; and, if so, how may this be done?

We have attempted to deal with the complexity of the behavioral phenomena in these stress experiments by having two psychiatric observers watch the entire procedure through a one-way vision screen. They kept detailed observational notes and, in addition, made independent ratings of the intensity of anxiety, anger, and depression during each period every day. We attempted to determine whether the observers tended to agree in their ratings of the various affects. In order to get a comprehensive evaluation of this question, we analyzed our data in several ways; all of these definitely pointed in the direction of considerable interrater agreement.

It appears that two observers can independently reach a rather high degree of agreement not only on the presence or absence of anxiety, anger, and depression but also on the extent to which each of these is being experienced by the subject. Some of the main points in this reliability analysis were as follows: 1. Approximately one-third of the time the two raters were in exact agreement on the level of affect, making their estimations on a 19-point scale. 2. The two raters were within one unit of each other more than 70% of the time. 3. They were

almost never more than 3 units apart. 4. Correlation of the two raters across all occasions was very high. 5. In judging which of the three affects was predominant during a given period, they were again in highly significant agreement. 6. Similarly, in judging direction of affect change from one period to the next, they were in very high agreement. 7. The mean level across all occasions of each rater for a given affect was very similar to that of the other rater. Taking all these findings together, we have reason to believe that we are dealing with phenomena which, though complex, are reliably identifiable and quantifiable.

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REFERENCES

1. Grinker, R. R., and Spiegel, J. P.: *Men Under Stress*, New York, The Blakiston Company (Division of Doubleday, Doran & Company), 1945.
2. Persky, H.; Gamm, S. R., and Grinker, R. R.: Correlation Between Fluctuation of Free Anxiety and Quantity of Hippuric Acid Excretion, *Psychosom. Med.* 14:34, 1952.
3. Persky, H.; Grinker, R. R.; Hamburg, D. A.; Sabshin, M. A.; Korchin, S. J.; Basowitz, H., and Chevalier, J.: Adrenal Cortical Function in Anxious Human Subjects, *A.M.A. Arch. Neurol. & Psychiat.* 76:549, 1956.
4. Basowitz, H.; Persky, H.; Korchin, S. J., and Grinker, R. R.: *Anxiety and Stress: An Interdisciplinary Study of a Life Situation*, New York, The Blakiston Company (Medical Division of McGraw-Hill Book Company, Inc.), 1955.
5. Tomkins, S. S., and Tomkins, E. J.: *The Thematic Apperception Test: Theory and Technique of Interpretation*, New York, Grune & Stratton, Inc., 1947.
6. Cronbach, L. J., and Meehl, P. E.: Construct Validity in Psychological Tests, *Psychol. Bull.* 52:281, 1955.
7. Grinker, R. R.; Korchin, S. J.; Basowitz, H.; Hamburg, D. A.; Sabshin, M.; Persky, H.; Chevalier, J. A., and Board, F. A.: A Theoretical and Experimental Approach to Problems of Anxiety, *A.M.A. Arch. Neurol. & Psychiat.* 76: 420, 1956.
8. Hunt, W. A.; Wittson, C. L., and Hunt, E.: A Theoretical and Practical Analysis of the Diagnostic Process, in *Current Problems in*

Psychiatric Diagnosis, Proceedings of the 41st Annual Meeting of the American Psychopathological Association, edited by P. R. Hoch and J. Zubin, New York, Grune & Stratton, Inc., 1953.

9. Hunt, W. A.; Wittson, C. L., and Burton, H. W.: A Validation Study of Naval Neuropsychiatric Screening, *J. Consult. Psychol.* 14:35, 1950.

10. Raines, G. N., and Rohrer, J. H.: The Operational Matrix of Psychiatric Practice: I. Consistency and Variability in Interview Impressions

of Different Psychiatrists, *Am. J. Psychiat.* 111: 721, 1955.

11. Bruner, J., and Tagiuri, R.: The Perception of People, in *Handbook of Social Psychology*, edited by G. Lindzey, Cambridge, Mass., Addison-Wesley Publishing Company, Inc., 1954, Vol. II, p. 634.

12. Heynes, R., and Lippitt, R.: Systematic Observational Techniques, in *Handbook of Social Psychology*, edited by G. Lindzey, Cambridge, Mass., Addison-Wesley Publishing Company, Inc., 1954, Vol. I, p. 370.

Relation Between Fine and Gross Psychomotor Movement in Schizophrenia

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It has long been known that disorders of gross motility are common in schizophrenia. Although significant distortions of movement are by no means to be found in the behavior of all schizophrenic patients, they are observed regularly in a large proportion of cases, taking such familiar forms as posturing, over- and underactivity, stereotypy, and so on. It has also been known for some time, or at least strongly suspected, that defects in motility might also be observed in certain fine psychomotor actions by schizophrenic persons in their performance of such activities as the speed of initiating a response, the tempo of repetitive response, the dextrousness of response, etc. The extensive literature relating to the experimental demonstration of these phenomena has recently been reviewed by King,^{3,4} and new data have been added further confirming their existence. An obvious question arises from this body of information which has not yet been the subject of direct experimental study: What is the relationship which exists between the disturbance of gross and that of fine psychomotor activity when the disorders are found concurrently within the same schizophrenic population?

When examining this problem, one must not fail to make a clear distinction at the outset between gross and fine psychomotor movement patterns as they would occur in the normal person. This usual, and useful, distinction has been described in detail by Seashore⁷ and, in essence, typifies fine psychomotor activity as that in which the factor of strength is secondary to speed or precision or both, such as the small limb

movements of typewriting or of benchwork, while gross psychomotor performance is that which involves relatively nonprecise but more total or more powerful activity or both, such as walking or dancing. The description of both types of activity as movement should not lead to the assumption that they are necessarily related activities of the organism. The experiments of Seashore⁷ and others have demonstrated that, indeed, they are not. It is common to find that only a low correlation exists among different types of psychomotor performance, despite a popular tendency to regard all forms of movement as being similar or closely related phenomena. Actually, the reverse is somewhat nearer the truth, for there is considerable independence evident among the different types of psychomotor performance of which the human is capable. The term movement describes a very general form of animate responsiveness, but a high degree of specificity exists, depending upon just what the movement in question may be. The broad division of movement patterns into the classes of fine and gross is one subgrouping which has been demonstrated experimentally to be valid for normal subjects,⁸ and it has therefore been employed here as a primary approach to the study of disordered motility in schizophrenia.

There is no reason to assume that these two main forms of human psychomotor activity, so demonstrably separate in the normal, should somehow become fused in the presence of schizophrenia. Yet something of the sort might seem to occur, since we know that both types of activity are affected to some extent by the presence of psycho-

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sis.^{2,3,6} The intervening disease process might be strong enough to order the two in a similar way, or, otherwise stated, each activity might become sufficiently related to an extraneous factor (schizophrenia) to become correlated, seemingly with one another. To test this question directly and experimentally, observations have been made upon both aspects of psychomotor performance—of fine and gross movement patterns—within the same schizophrenic populations, and the data obtained under these circumstances form the body of this report.

Method

Although our question may be put simply, the choice of methods to be employed in an attack upon it presents some difficulty. As has been stated, the variety and complexity of movement of which the human is capable is tremendous, and, by its heterogeneity, it is clear that it cannot be measured adequately or sampled in its entirety by any single type of activity. For this reason the experiments to be described here have employed a variety of movement measures of both fine and gross activity which have been carefully selected to represent as well as possible the larger number of related activities from which they have been drawn.

Fine Psychomotor Movement.—To obtain a reasonably balanced estimate of fine psychomotor performance by schizophrenic subjects, three different tests have been selected to represent relatively independent qualities of such activity: (1) reaction time; (2) speed of tapping, and (3) finger dexterity. The basis for this selection has been described in detail elsewhere^{3,4} and rests upon a factor analysis of the performance data of normal subjects engaged in a wide variety of psychomotor tasks. One of the uses of this mathematical method is to select a few tests which best represent a larger series from which they have been drawn. The results of an analysis of normal performance upon a variety of psychomotor tests have thus revealed the presence of three essential trends (basic vectors) which best serve to describe the total pattern of performance under study. As these factors—(1) speed of initiating movement, (2) speed of continued oscillatory movement, and (3) movement dexterity—are in close agreement with the results obtained in similar analyses by independent investigators,⁵ they have been accepted as representative qualities of fine psychomotor performance, and the three test methods most closely associated with these basic vectors have been selected as the test instruments of choice. Since the intercorrelation of performance on these tests is low (<0.44),

they may be assumed to be measuring relatively independent aspects of fine psychomotor performance. Briefly, the tests and their scores are as follows:

Reaction Time (Jump): The subject was instructed to lift his right hand from a rest at the onset of an auditory signal (buzzer, 55 db.) and to cross and press a key (placed 10.5 in. distant) as quickly as possible. The score for the test is the average time (in 0.01 second) which elapsed between the onset of the signal and the completion of response in 10 trials.

Speed of Tapping: A count was registered of the number of taps by the right index finger which could be made in a five-second interval between two metal plates (two in. square) placed 14 in. apart in a horizontal plane and separated by a $\frac{1}{2}$ in. midline barrier. Scores are given as the average number of taps made per five-second interval on five trials.

Finger Dexterity: A count was made of the number of successfully completed combinations and insertions of small metal pieces which could be assembled according to instruction within a fixed time interval. This is the Assembly test, taken directly from the Purdue Pegboard test of Finger Dexterity,⁶ and it was given and scored by the standard method. The score is the number of pieces assembled within the standard one-minute interval allowed.

Gross Psychomotor Movement.—The selection of tests which might serve as appropriate measures of gross activity by human subjects is not easily accomplished, owing in part to a paucity of information and relevant experimental study of this topic, and in part to limiting factors in the population to be observed. Although the eye easily observes gross movement patterns in human subjects, the notation of these actions in symbolic characters remains a most difficult problem, and proper tools and methods are lacking for recording active bodily movements so that they may later be analyzed quantitatively. A few simple methods have been devised by those attempting to investigate problems of this sort, however, and two such indices of gross movement, Time-Sampling Recording and Pedometer Recording, which are applicable to schizophrenic populations have been employed as sample measures of gross activity in this study. To these has been added a measure of active strength, the Handgrip test, which, although it is unquestionably a more isolated fragment of body activity, might add a useful indication of the intensity component of gross psychomotor performance. Briefly, the tasks and their scores are as follows:

Time-Sampling Recording: Kinder⁷ recently has adapted the time-sampling methods often em-

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played in the study of animal behavior to the observation of movement and movement patterns by psychotic subjects. In essence, the method is to place the subject in a situation appropriate for eliciting behavior of a spontaneous sort, to observe the subject continuously through a one-way vision mirror, and to note continuously on a moving paper strip the type and duration of the spontaneous activity observed. The activity of schizophrenic subjects has been observed by means of this technique* as they responded to the stimulation of being placed in a mock waiting room to await appointments for other examinations. The complete details of the behavior-recording and scoring methods used may be found in the original report by Kinder et al.²; for present purposes, it may be described briefly as an activity score based upon an evaluation of the energy expenditure involved in whatever behavior was seen. The coded observational records include a notation of practically every movement or observable behavior change taking place during the test period, such as changes in location (standing, pacing, dancing, etc.), attention to objects (use, manipulation, transport, etc.) and self-directed behavior (grooming, shifts of limb position, etc.). A total activity score is derived as an index of the amount of activity observed during two 20-minute periods of study for each subject.

Pedometer Recording: An estimate was made of the amount of walking activity by schizophrenic subjects during a 24-hour period by means of a pedometer, or "walking meter." This device is intended to record each step taken by its wearer and to present at any given time an approximate count of the number of steps taken since it was set at zero.† While it is admittedly a crude measure, since it records only step motion, the device offers a convenient method for at least approximating the amount of locomotor activity by a subject over a given period of time. The recording instruments were worn by our schizophrenic subjects for a standard 24-hour period (8 a. m. to 8 a. m.,) and the number of steps per hour, derived from the total, constitutes the score for this measure of gross activity.

Handgrip Test: The familiar dynamometer, or strength-of-grip-recording apparatus, was employed for this test. The instrument used was of the Smedley type,‡ with the distance to be spanned between the base of the thumb and the fingers set at 6 cm.⁶ The subject made two test grips

with the right hand, the two trials being separated by a two-minute rest period. The averaged score, in kilograms, for these two observations constitutes the Handgrip score given in this study.

Results

Three different groups have been studied, each comprised of schizophrenic subjects matched for diagnosis, age, and length of hospitalization. There is no significance attached to the division of subjects into three groups other than temporal and practical considerations. They are intended to represent generally comparable patient populations with respect to diagnosis, age, and duration of illness. The diagnosis of schizophrenia was, in all instances, well established, and no patient has been included in the series who had not been committed to the care of a state institution with this diagnosis for a period of at least three years. The number of subjects in each group (A, B, and C), their average age, and length of hospitalization is shown in Table 1.

The mean score and standard deviation achieved by each group on the tests of fine psychomotor movement are also shown in Table 1. An inspection of the scores obtained makes it evident that all three test groups perform at a level closely approximating that of chronic schizophrenic patients, as given by King,³ and clearly below that of normal persons of the same age. The test groups differ slightly, but not significantly, from one another, as would be expected. Since it is not our purpose here to compare subject groups, rather, to compare types of performance within a given group,

TABLE 1.—Means and Standard Deviations for All Groups on the Tests of Fine Psychomotor Movement

Groups	A	B	C	Chronic Schiz. (3)	Normal (3)
Fine Psychomotor tests					
Reaction time (jump), M	92.1	101.7	87.6	87.0	46.4
0.01 sec., <i>σ</i>	47.6	29.6	44.6	42.1	8.45
Speed of tapping, M	12.2	13.7	11.1	12.0	22.6
taps/5 sec., <i>σ</i>	3.76	6.08	5.30	6.31	3.62
Finger dexterity, M	22.8	25.5	21.1	22.0	41.1
units/min., <i>σ</i>	8.19	7.73	7.27	8.68	6.31
No. of subjects	51	36	63	90	194
Length of hosp., yr.	8.1	7.8	9.3	9.1	
Average age, yr.	42.8	43.8	42.6	42.9	42.2

* Dr. Elaine Kinder and her co-workers² furnished these observations and activity scores.

† Aristo pedometer, No. 99, Compass Instrument & Optical Co., Inc., New York.

‡ Hand dynamometer, No. 205, Lafayette Instrument Co., Lafayette, Ind.

these small differences in mean performance by different sample populations will be unrelated to the main line of investigation pursued.

Group A: Time-Sampling Recording.—The first comparison of fine and gross movement measures within a schizophrenic population was made with Group A. This group, of 51 subjects, was ordered (ranked) in terms of the total activity score obtained by the Time-Sampling-recording techniques, and then subdivided into the three classes of the least active, moderately active, and most active subjects by this criterion. Table 2 presents the mean activity scores when the total group is thus subdivided into thirds, together with the fine psychomotor performance scores for these subgroups. An inspection of the scores obtained reveals little difference in the performance of any of the three subgroups. There is a slight retardation in Reaction Time (jump) scores for the least active group, but all other scores indicate approximately the same level of fine psychomotor performance for each activity group. A statistical comparison of the extreme groups (least and most active) by the method of critical ratio indicates no significant differences in fine psychomotor performance.

Group B: Pedometer Recording.—We may compare, in a similar way, the subjects of Group B by ranking the 36 subjects in terms of the Pedometer scores obtained (steps per hour) and then subdividing them

into the three classes of the least active, moderately active, and most active subjects. Table 3 presents the mean scores for the total group divided by this criterion, together with the scores of fine psychomotor performance obtained from these subgroups. An inspection of this Table reveals a slight but nonsystematic trend. As one passes over the scores from the least active to the most active subgroup, the Reaction Time (jump) scores are seen to be slightly slower, the Speed of Tapping scores first increase and then decrease, and the finger dexterity scores indicate a progressively greater slowing in performance. There is a tendency, therefore, for somewhat retarded fine psychomotor performance to be associated with the more active patients as judged by this criterion. A comparison of the extreme groups (least and most active) by critical ratio, however, indicates that these differences in performance do not reach the 0.05 level of statistical significance.

Group C: Handgrip Test.—The subjects of Group C were ranked in terms of the scores achieved on the Handgrip test and divided into the three classes of the least active, moderately active, and most active subjects. Sex differences are usually great in performance on this type of test; therefore the data have been computed separately for male and female subjects. Table 4 presents the mean scores for the male and female subjects with each sex group divided into thirds on the basis of the Handgrip test score, together with the scores of fine

TABLE 2.—Means and Standard Deviations for the Tests of Fine Psychomotor Movement: Group A Divided into Thirds by Time-Sampling Activity Score Criterion

Subgroup	N	Activity Score	Reaction Time (Jump) 0.01 Sec.	Speed of Tapping, Taps/5 Sec.	Finger Dexterity, Units/Min.
Least active	17	116	M 104 σ 58.3	12.1 4.78	23.0 7.35
Moderately active	17	257	M 87.0 σ 42.4	12.4 3.90	25.0 7.97
Most active	17	451	M 86.0 σ 37.2	12.1 2.07	21.0 8.74

TABLE 3.—Means and Standard Deviations for the Tests of Fine Psychomotor Movement: Group B Divided into Thirds by Pedometer Score Criterion

Subgroup	N	Pedometer Score, Steps/Hr.	Reaction Time (Jump), 0.01 Sec.	Speed of Tapping, Taps/5 Sec.	Finger Dexterity, Units/Min.
Least active	12	52.4	M 80.7 σ 29.7	10.8 6.85	23.3 8.04
Moderately active	12	149.5	M 82.2 σ 17.4	12.3 4.77	21.9 7.18
Most active	12	399.0	M 91.5 σ 37.1	10.7 6.34	18.5 7.12

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TABLE 4.—Means and Standard Deviations for the Tests of Fine Psychomotor Movement: Group C Divided into Thirds by Handgrip Score Criterion

Subgroup	N	Handgrip Score, Kg.		Reaction Time (Jump), 0.01 Sec.	Speed of Tapping, Taps/5 Sec.	Finger Dexterity, Units/Min.
Male subjects						
Least active	8	29.0	M	121.3	9.9	17.2
			σ	88.4	5.83	5.09
Moderately active	7	43.3	M	66.1	13.7	22.4
			σ	13.7	5.36	7.41
Most active	8	53.5	M	60.2	13.6	26.9
			σ	9.47	5.51	7.20
Female subjects						
Least active	13	19.1	M	92.7	10.4	17.6
			σ	40.3	5.18	5.80
Moderately active	14	24.6	M	95.8	10.1	20.5
			σ	32.1	4.96	6.26
Most active	13	32.8	M	81.4	10.3	23.5
			σ	19.1	4.20	7.31

psychomotor performance for each subgroup.

An inspection of the mean scores of Table 4 reveals a tendency for the less active subjects, by this criterion, to be relatively slower in performance on the fine psychomotor tasks and for the more active subjects to be relatively faster in their fine psychomotor performance. This may be seen most clearly on the scores for Finger Dexterity for both male and female groups. It is also apparent for the male group on Reaction Time (jump) test scores and, to a less extent, in the Speed of Tapping scores. The female group exhibits the same tendency, less clearly, for Reaction Time (jump) scores, but does not do so on the Speed of Tapping test. A comparison of the extreme groups (least and most active) for each sex group by means of the critical ratio shows the differences to be significant at the 0.05 level of confidence for the Finger Dexterity scores for each group; all other differences noted in test scores are nonsignificant.

Comment

From these findings it would appear that no strong relationship exists between the fine and gross psychomotor movement patterns of schizophrenic subjects. Within the limits

of the ability of our sample tests to represent these broad factors, the data show little evidence of a linkage, either genuine or spurious, between the two types of performance. This finding is, of course, in keeping with what is known of the relation of these two forms of psychomotility among normal subjects, unaffected by psychosis. It would indicate that an intervening process such as schizophrenia, although known to exert an influence on psychomotor responsiveness at both the fine and the gross level of discourse, does not necessarily affect them in a similar or strongly correlated way. It may seem remarkable that a spurious correlation did not arise in our data between the scores of fine and gross psychomotor movement in view of the fact that each type of observation has demonstrated its ability to discriminate the psychotic from the normal and to differentiate some sort of gradations of the degree of behavior disorder.^{4,6} This lack of even a spurious correlation may rest in the fact that the fine psychomotor measurement techniques have been found to differentiate degrees of schizophrenic disturbance along a roughly linear continuum, in which the greatest retardation is associated with markedly disordered behavior and the least retardation with the least disordered behavior. Gross motility, by contrast, deviates in two (opposite) directions from a midpoint of average activity—tending toward a hypoactivity in one patient and a hyperactivity in another. Whatever the possible explanation, it seems clear that there is no more evidence of a fusion of the dimensions of "speed" and "power" in movement in the presence of chronic schizophrenia than can be found in the performance of non-schizophrenic subjects engaged in similar activities.

One trend which has become apparent in our data calls for further comment—the tendency of the Handgrip test scores to show a rough paralleling with the scores obtained on fine psychomotor activity. Although the groups compared on the basis of the Handgrip criterion were found to differ

significantly in but one context (the Finger Dexterity scores), an inspection of the data in Table 4 indicates a nonsignificant but consistent shift in performance in the same direction for some of the other tests employed. The inclusion of the Handgrip test in the experimental battery as a measure of gross psychomotor movement was admittedly debatable, as it is a rather peripheral measurement, not normally considered to be or employed as an index of gross psychomotor activity. It was decided to include it to obtain some idea of the "power" produced upon request by instructions given a patient as opposed to other measures of "power" output by the patient not in response to request but more spontaneous in nature (e. g., by pedometer count). On descriptive grounds alone, then, this task is the most similar in form to the tests of fine psychomotor performance; that is, an action immediately consequent upon request and of a limited duration, as opposed to the non-instructed and longer duration of the other measures of gross psychomotor activity. In terms of the data obtained, this test has also been found the most likely of the gross indices to parallel observations made by tests of fine movement. This paralleling is rendered the more interesting by the fact that the average score for the group of schizophrenic patients taken as a whole does not differ significantly from the average scored on the same test by a nonpsychotic group of comparable age and sex composition.¹⁰ It has been claimed, without much in the way of validation, that handgrip is a good measure of motivation or drive.¹ As such it might differentiate a schizophrenic population along a unidirectional continuum, rather than the bidirectional situation of over- and underactivity on both sides of the average which is characteristic of our other measures of gross activity. This could, in turn, give rise to a spurious correlation. Too little is known at present to allow proper evaluation of the meaning of this finding, but it can serve as a positive focus for further

investigation, from which more definitive information may be gained.

Summary

Significant distortions of gross motility are known to exist among schizophrenic patients,⁶ and marked defects have also been demonstrated to occur in the fine psychomotor movement patterns of schizophrenic persons.³ This study is concerned with examining the relationship which exists, if any, between these forms of disordered psychomotor activity.

Tests of fine psychomotor performance (Reaction Time [jump], Speed of Tapping, and Finger Dexterity) and gross psychomotor behavior (Time Sampling, Pedometer, and Handgrip) were applied to the same populations of schizophrenic patients, and the data obtained were analyzed for indications of correlated distortion.

No evidence was obtained to indicate that the two types of psychomotor disorder are affected in a related way in the presence of chronic schizophrenia. Each seemed to be affected within its own dimension, and the tests in no way appeared to be measuring simply different aspects of the same process. Each type of appraisal appears to have diagnostic value in its own right.

Some degree of relationship was found to exist between schizophrenic performance on the Handgrip tests, used as a measure of gross motility, and performance on the fine psychomotor tests. A significant relationship was obtained between scores on this test and Finger Dexterity scores, with an accompanying nonsignificant but consistent shift in performance on some of the other tests employed. A possible basis for this partial relationship is discussed.

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REFERENCES

1. Heron, A.: The Objective Assessment of Personality Among Factory Workers, *J. Social Psychol.* 39:161-185, 1954.
2. Kinder, E. F., and others: Activity: A Time-Sampling Study, in *Studies in Topectomy*, edited

Vol. 79, April, 1958

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by N. D. C. Lewis and others: New York, Grune & Stratton, Inc., 1956, Chap. 8.

3. King, H. E.: *Psychomotor Aspects of Mental Disease: An Experimental Study*, Cambridge, Mass., Harvard University Press, 1954.

4. King, H. E.: *Psychomotor Techniques*, in *Experimental Abnormal Psychology*, edited by J. Zubin, New York, Columbia University Press, 1957, Chap. 13.

5. Miles, W. R.: *Simultaneous Right- and Left-Hand Grip*, in *Methods in Medical Research*, Chicago, Year Book Publishers, Inc., 1950, Vol. 3, pp. 154-156.

6. Noyes, A. P.: *Modern Clinical Psychiatry*, Ed. 4, Philadelphia, W. B. Saunders Company, 1953.

7. Seashore, R. H.: *Work and Motor Performance*, in *Handbook of Experimental Psychology*, edited by S. S. Stevens, New York, John Wiley & Sons, Inc., 1951, Chap. 36.

8. Seashore, R. H.; Buxton, C. E., and McCullom, I. N.: *Multiple Factorial Analysis of Fine Motor Skills*, *Am. J. Psychol.* 53:251-259, 1940.

9. Tiffin, J., and Asher, E. J.: *The Purdue Pegboard: Norms and Studies of Reliability and Validity*, *J. Appl. Psychol.* 32:234-247, 1948.

10. Miles,⁶ p. 156.

Relation of Emotional Responses and Changes in Plasma Hydrocortisone Level After Stressful Interview

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Various natural and experimental situations generally considered to be psychologically stressful are capable of influencing the activity of the adrenal cortex. Auto racing,¹ competitive rowing,² paratroop training,³ anticipation of surgery,⁴ and college examinations⁵ produce a significant diminution in the blood eosinophil level, and experimental frustration raises the urinary uric acid-creatinine ratio.⁶ Following the introduction of more direct estimates of adrenocortical activity by measurements of plasma hydrocortisone level and urinary hydroxycorticosteroid excretion, participation in an accident, taking a college examination,⁷ being admitted to a mental hospital during acute emotional disturbance,⁸ and taking part in a stressful psychiatric interview^{9,10} have also been shown to increase adrenocortical functioning. It is generally taken for granted that these are all situations that most people find difficult and trying, and that some find

very disturbing. Yet it is well known that there are many individual responses to such situations. There are many variables in human behavior which might be specifically related to the secretory activity of the adrenal cortex; yet there has been very little systematic exploration of such relationships. Clues from recent investigations indicate a number of psychological factors which may be of special significance for the problem of adrenocortical activation under stressful conditions.

Bliss and his associates,⁷ for example, observed that "states of emotional disturbance and heightened anxiety are routinely, although perhaps not invariably, associated with small but significant elevations in the level of adrenocortical steroids in the plasma." Similarly, Hetzel and his colleagues⁹ reported that "feeling states described by the subjects as apprehension or dread and exhilaration or excitement have been found to be associated with increases in 17-hydroxycorticoid excretion." Board and his co-workers⁸ noted that patients who were newly admitted to a mental hospital showed a correlation between the degree of subjectively experienced emotional distress and hydrocortisone plasma level.

Price, Thaler, and Mason¹¹ have recently found that early morning hydrocortisone levels were significantly elevated in a group of patients anticipating chest surgery. In addition, they found significant correlations between emotional discomfort-involvement ratings and early morning hormone levels. Basing their psychological findings on interview and Rorschach data, they concluded:

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Now at the Institute of Psychiatric Research, Indiana University Medical Center (Dr. Persky). Now at the National Institute for Mental Health, Bethesda, Md. (Dr. Hamburg). Now at the Department of Psychiatry, Upstate Medical Center, State University of New York College of Medicine, Syracuse, N. Y. (Dr. Basowitz).

This study was carried out as part of a program of research into the psychosomatic organization of anxiety and was supported by the U. S. Army under Contract No. DA-49-007-MD-469 through the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, and by the State of Illinois Mental Health Fund.

A concept of how anxious a patient appeared to the observers did not prove as useful as the extent to which a patient made active emotional participation with his environment; i. e., his degree of emotional involvement appeared to be a more valuable operational concept in predicting the steroid values than anxiety alone.

The major conclusion suggested by our findings is that the response of the pituitary-adrenocortical system is related to emotional processes, and, further, that it is probably not associated with a single specific emotional state, such as anxiety or fear, but, rather, with a number of emotional states that have the relatively undifferentiated component of distress-involvement.

This conclusion, as well as the study from which it was derived, is particularly interesting because it is addressed directly to the question of the specific nature of the relationship between psychological and adrenocortical functions. These investigators have followed the main trend evidenced in the previous literature in selecting emotions rather than other psychological processes as the focal point for their study. Certainly the predominant suggestions from previous work have pointed toward emotional disturbance as a probable correlate of adrenocortical activity. This group has gone further, however, in that it has attempted differentiation within the field of emotions. The particular question raised and partially answered is this: "Is adrenocortical activity linked uniquely with one particular type of emotional response, or is it related to a wide variety of emotional responses?" Our present study is also directed toward this question.

In the course of a larger, multidisciplinary study on the psychosomatic organization of anxiety,¹² the plasma level of the adrenocortical hormone hydrocortisone¹⁰ and a number of psychological indices¹³ were determined before and after a stressful psychiatric interview. The present paper reports a number of significant relationships between the changes occurring in hormone level and in each of the assessed psychological parameters under the impact of a stress interview.

Subjects, Experimental Design, and Methods

The subjects, experimental design, and methods of this study have been described in detail in other papers.^{10,12} They will be briefly summarized below.

The subjects were a group of 22 anxiety-prone patients hospitalized on the psychiatric service of a general hospital. Nineteen of the participants in this study completed the experiment. For 17 of these 19 subjects complete hydrocortisone data are available.

Diagnostically, the patient group consisted chiefly of neurotics, a few borderline patients, but no overtly psychotic patients. Their ages ranged from 20 to 58 years, with a mean of 39 years. All the subjects were in good physical health.

On each of four successive days three blood samples were drawn from each patient: the first at 9:00 a. m. (*Pre*), the second at 10:30 a. m. (*Post*), and the third at 2:30 p. m. (*Extra*). After an initial day of familiarization with the laboratory, personnel, and procedure (preexperimental day), there were three stress interview (S. I.) days. On each of these S. I. days, a disturbing interview, lasting about 30 minutes, was interposed between the *pre* and *post* blood samples. The interview attempted to evoke emotional distress in the patients by vigorously exploring personal problems known from earlier diagnostic study to be disturbing to the patient.

The emotional status of the anxious patients was independently assessed by two psychiatric observers. The method of arriving at the affective ratings will be reported separately,¹² but it is appropriate to give some information about it here. Each subject was rated along a seven-point scale for the intensity of anxiety, anger, and depression which he experienced during the time span of each experimental period. Ratings could be made to the nearest one-third of a scale unit. Ratings were made for the pre-stress, during-stress, and post-stress periods. The ratings were made by the psychiatrists while observing the entire experimental procedure through a one-way-vision screen. The estimates were based on the patient's verbal report of his emotional experience at the time, augmented by such nonverbal signs as facial expression and bodily movements. The evidence for the ratings came from two sources: (1) direct observation of the subject throughout the experiment, and (2) psychiatric interviews with the patient before and after the experimental stress, designed specifically to elicit information about the patient's experience during each period of the experiment. The psychiatric observers saw and heard these evaluation interviews, as well as the stress interview. Their final rating for each affect was a consensus agreed upon by the two observers.

The interrater reliability achieved a level of confidence which was statistically significant.¹⁸

Certain criteria were employed to characterize each rated affect and to help with the quantification of the rating estimate. The patient communicated to the observers both verbally and nonverbally that he was probably experiencing a certain type of feeling. While we do not believe it is possible to define these feeling experiences precisely, it is possible to give a series of simple descriptive terms which indicate meaningfully the range of emotional experiences included within each affect. In each instance the terms commonly used to indicate a certain type of emotional experience fall into a kind of spectrum, ranging from a mild form of the experience to a very intense form. Within this spectrum, the various terms overlap considerably; but as one progresses through the list of terms applicable to each affect, gradually increasing intensity is denoted, viz.:

Anxiety: apprehension, foreboding, danger, dread, panic

Anger: annoyance, irritation, resentment, hostility, rage, fury

Depression: sadness, regret, discouragement, dejection, gloom, despondency, despair

The scale of intensity on which each affect was estimated ranged from 0 to 6: Zero (0) indicates that the particular feeling was absent; 1 means distinct but not impressive; 2, impressive; 3, intense; 4, unusually intense; 5, extremely intense, and 6, most extreme ever reported.

An estimate of over-all emotional distress was obtained through the use of a combined affect rating. This was simply a summation of the ratings for anxiety, anger, and depression. Although this is a crude approximation, it has proved useful in clarifying certain relationships.

The chemical methods employed in the present study have been referred to in a preceding paper.¹⁰ It should be explained why the plasma hydrocortisone level was chosen as the index of adrenocortical function rather than such indices as urinary hydroxycorticosteroid excretion, corticotropin responsivity, etc. No one of these indices is completely satisfactory; even the turnover of hydrocortisone-4-C¹⁴ is not a perfect index, since it is a static measure, indicative of the rate of production for the time of day at which the tagged molecule is administered. The plasma level of hydrocortisone was chosen as the index for intercorrelation with the psychological parameters, for the following reasons. 1. The plasma level represents a balance between the rate of production and destruction of the hormone by the body, and hence constitutes a conservative estimate of any over-all increase or decrease in glandular activity. Since removal of hydrocortisone from the plasma in anxious patients is faster than in normal subjects,

a small increase in plasma hydrocortisone level may reflect a much greater increase in the quantity of hormone production. Turn-over studies employing hydrocortisone-4-C¹⁴ have demonstrated that the production rate of hydrocortisone may increase six-fold, while the plasma level may not even double.¹⁷ 2. Blood samples may be obtained almost instantly and hence a point in time may be fixed. 3. Blood samples constituted the most practical index under the realistic circumstances of the total experimental design.

Results

Change in Hydrocortisone Level in Relation to Degree of Emotional Response.

One of the central questions in this study was whether, under the impact of personal threat, emotional responses tended to be associated with adrenocortical responses. We used the stress interview as a means of presenting a personal threat, the observers' ratings as an estimate of the emotional response, and the plasma hydrocortisone level as an index of the adrenocortical response. Our prediction was that a relatively intense, prolonged emotional disturbance would often be associated with a rise in hydrocortisone—or at least a diminution of the usual diurnal fall. While the hypothesis clearly stated that anxiety and anger would be associated with a tendency toward hydrocortisone elevation, we were quite uncertain as to what the relation of depression and hydrocortisone might be. Similarly, we wondered whether we could detect affect-steroid relationships simply by focusing on the patient's response during the S. I. or after the S. I. We therefore decided to carry out a series of related, and to some extent overlapping, analyses in order to explore the problem systematically. Consequently, we undertook analyses in terms of several time spans and several affective indices in an effort to determine whether any affect-steroid relationships would emerge consistently.

The stress interview was intended to evoke a striking emotional response lasting one to several hours. The intention was primarily to stimulate anxiety, but it was anticipated that anger and depression would frequently be evoked as well, since the

TABLE 1.—Change in Plasma Hydrocortisone Level (Post Minus Pre) Following a Stress Interview Administered to Each of Seventeen Anxious Patients on Three Consecutive Days

Occasion *	Plasma Hydrocortisone Level †								
	Anxiety			Anger			Depression		
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change
Day of greatest increase in affect	17.9±6.0	15.3±7.0	-2.6±8.3	17.0±6.4	15.8±7.2	-1.8±8.2	18.5±6.2	14.7±5.4	-3.7±6.8
Day of median increase in affect	18.7±6.1	15.4±6.0	-3.3±5.4	21.4±6.9	15.6±5.6	-5.9±7.5	18.2±6.5	16.4±7.4	-1.8±7.3
Day of least increase in affect	22.0±7.5	13.6±5.5	-8.4±8.5	19.5±6.6	13.0±5.4	-6.5±7.3	21.9±7.0	13.2±5.2	-8.7±7.9

* On the basis of Post minus Pre values for affect.

† Mean±standard deviation, in micrograms per 100 cc.

interview consisted of a vigorous exploration of conflict areas in the personal life of the patient. As the research proceeded, abundant evidence accumulated that the stress interview did not always achieve its intent.¹⁶ Frequently the patient experienced little, if any, emotional response to it, and sometimes there was actually relief, rather than distress. It therefore seemed logical to scan the data for instances in which the basic intent was most clearly achieved; that is, instances in which a relatively great increase in intensity of anxiety, anger, or depression was observed in association with the stress interview. In order to use the subject as his own control, within the limits imposed by the fact that there were only three S. I. days, we ranked the affective responses for each patient as follows: The day of greatest *pre* to *post* increase in anxiety was listed first; then the day of median *pre* to *post* increase in anxiety, and, finally, the day of

least *pre* to *post* increase in anxiety. The same was done for anger, for depression, and for the sum of all affects combined. The actual day on which a given response occurred varied greatly; that is, the day of greatest increase in anxiety might occur on the third S. I. day for some patients, on the second S. I. day for other patients, and on the first S. I. day for the remainder. The *pre* to *post* change in hydrocortisone level on the day of greatest, median, and least increase in affect rating was then calculated for the entire group (Table 1). An analysis of variance among the change scores for plasma hydrocortisone showed that change in each of the rated affects was significantly and linearly related to the change in hormone level (Table 2). It should be stated here that the affective variables are not independent of each other but, rather, are highly interrelated on occasions, and not necessarily by subjects (to

TABLE 2.—Analysis of Variance Among Changes in Plasma Hydrocortisone Level (Post Minus Pre) for Various Degrees of Change in Affect Ratings (Post Minus Pre)

Source of Variation	df	Anxiety Change		Anger Change		Depression Change		Combined Affect Change	
		Mean Square	F	Mean Square	F	Mean Square	F	Mean Square	F
Between subjects	16	77.11	1.67	77.11	1.55	77.11	1.70 *	77.11	1.75 *
Between degrees of change in affect ratings	2	170.25	3.69 †	111.15	2.23	220.20	5.11 †	205.66	4.68 †
Linear	(1)	285.94	6.19 †	189.65	3.80 *	213.00	4.95 †	355.88	8.09 †
Quadratic	(1)	34.56	1.18	32.64	0.65	227.40	5.28 †	35.44	1.26
Error	32	46.18		49.88		43.06		43.97	
Total	50								

* Significant at the 10% level.

† Significant at the 5% level.

‡ Significant at the 1% level.

TABLE 3.—Relationship of the Change in Plasma Hydrocortisone Level (Post Minus Pre) Following a Stress to the Change in Combined Affect Ratings (During Minus Pre)

Occasion	Plasma Hydrocortisone Level *		
	Pre	Post	Change
Day of greatest increase in combined affect	18.9±6.1	16.6±7.1	-2.3±8.4
Day of median increase in combined affect	17.6±6.4	14.3±6.1	-3.2±6.3
Day of least increase in combined affect	22.1±7.1	13.4±5.1	-8.7±7.4

* Mean±standard deviation, in for 17 subjects micrograms per 100 cc.

be reported in a later paper). The extent of the relationship is quite similar for all three affects, although it is slightly greater in the case of anxiety and depression ($F=6.19$ and 4.95 , respectively) than in the case of anger ($F=3.80$). When all three ratings are used together in a combined emotional rating (arrived at simply by adding the ratings for anxiety, anger, and depression), the relationship obtained is more highly significant than that for any single affect ($F=8.09$).

Thus, hydrocortisone change paralleled emotional change; and this relationship was not limited to a single, specific state like anxiety, but, rather, concerned a wide range of emotional disturbances. The results suggested that the over-all extent of disturbance may be the crucial factor. The time unit of study in this analysis was *pre* to *post* change in emotional state. This seemed to be a particularly meaningful time unit because (a) it gave a picture of the subject immediately before and immediately after the crucial change-agent had been applied and (b) it covered a sufficiently long span as to be comparable to the more significant disturbances of everyday life. However, the question arose whether the same sort of steroid-affect relationship might occur by examining other time units.

The time unit previously employed, *pre* to *post* change, was chosen on the assumption that the emotional impact of the stress interview must be of relatively long duration in order to exert significant effects throughout the organism. It may well be that briefer

periods of disturbance can produce significant changes in hydrocortisone levels. Since the affect ratings were obtained for *pre*, *during*, and *post* stress interview periods, the *pre* to *during* periods constituted the shortest time span observed. In order to determine the extent of relationship between the change in affect over this time span and the change in hormone level (*post* minus *pre*), the change scores for plasma hydrocortisone level (Table 3) were subjected to an analysis of variance (Table 4). The change in combined affect was chosen because in the preceding analysis of variance of Table 2 it bore the highest degree of relationship to the change in hormone level. Even with the shorter time span for affect change, the relationship between combined affect and hormone level change was significant and linear. It should be noted that some patients who manifested relatively high *during* affect levels also had high *post* levels, while others tended to drop off sharply in the *post* period. This analysis therefore included both transient and prolonged emotional responders and consequently did not give a decisive answer to the short-term question. It did show clearly that the affect-steroid relationship may be detected (within limits) by simply viewing the immediate emotional response to the stress (*during*) without reference to subsequent events (*post*).

In the previous analyses we have taken as our criterion of emotional response either

TABLE 4.—Analysis of Variance Among Changes in Plasma Hydrocortisone Level (Post Minus Pre) for Various Degrees of Change in Combined Affect Rating (During Minus Pre)

Source of Variation	df	Combined Affect Change	
		Mean Square	F
Between subjects	16	77.11	1.76
Between degrees of change in combined affect rating	2	206.63	4.71 *
Linear	(1)	247.32	5.63 *
Quadratic	(1)	165.94	3.78
Error	32	43.91	
Total	50		

* Significant at the 5% level.

the increase in affect rating from *pre* to *post* or from *pre* to *during*. It also appeared worth while to combine the *during* and *post* ratings (*during-and-post*) in order to get some estimate of the total impact of the stress, since it often happened that the subject's emotional distress could be observed from a short time after the beginning of the interview, through the remainder of the stress interview, and during the following hour of the *post* period. Therefore, one obtained the most comprehensive picture of emotional response to the stress by viewing both the *during* and the *post* period. The change in hormone level from the *pre* to the *post* period on the day of each subject's greatest increase in combined affect (*pre* to *during* plus *post*) was found to be significantly greater than on the day of each subject's least increase in combined affect ($t=2.18$; $P<0.05$). On the day of each patient's greatest *pre* to *during-and-post* rise in affect, the level of hydrocortisone remained significantly higher during the morning than on the day of least affect rise.

The preceding analyses indicated that a number of affects bore a significant relationship to plasma hydrocortisone level. The question remains whether any particular affect is more highly related than the others. The results of Table 2 did not support such a view. To examine further such a possibility, the changes in plasma hydrocortisone level for the entire group (*post* minus *pre*) on the day of each subject's greatest increase in affect were compared with the changes occurring on the day of least increase in affect. The differences in plasma-hydrocortisone-change scores were greatest for anxiety and least for anger, but, as in Table 2, these differences did not indicate a significantly greater relationship for any one affect. Since the various affects are highly interrelated, it should be realized that the relationship explored is one between the change in hydrocortisone level and a *set* of affective variables.

Further information about the relation of affect to hormone level may be obtained by

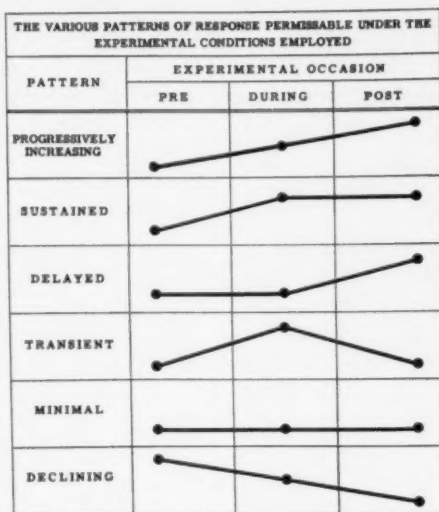


Figure 1

an examination of the pattern rather than the magnitude of these variables. The many possible permutations of the *pre*, *during*, and *post* affect ratings may be summarized by six patterns capable of defining an entire experimental occasion. Figure 1 graphically illustrates the various response patterns permissible. These patterns of emotional response will be described more fully elsewhere.¹³ In general, the "progressive rise" and "sustained" patterns represented the greatest response to the stress interview; the "minimal" and "declining" patterns represented the least response, and the "transient" and "delayed" responses were intermediate. The change in plasma hydrocortisone level on all subject-occasions on which the emotional response pattern is categorized as "progressively rising" and "sustained" was significantly greater than when the pattern was "minimal" and "declining" for each affect (Table 5).

The data presented thus far have considered the relationship between the change in affect and the change in hormone level for the group of subjects as a whole. It has generally been found that large increases in the group's affect are associated with significant increases in hormone level. It is pos-

TABLE 5.—Relation of Pattern of Emotional Response to Change in Hormone Level (Post Minus Pre)

Affect	Pattern of Emotional Response	Number of Subject-Occasions †	Plasma Hydrocortisone Level *			t	P ‡
			Pre	Post	Change		
Anxiety	"Progressive rise" + "sustained"	32	18.8±6.2	15.3±6.4	-3.5±7.9	1.72	<0.05
	"Minimal" + "declining"		21.7±8.1	13.6±4.8	-8.1±6.6		
Anger	"Progressive rise" + "sustained"	34	17.3±5.0	16.6±6.9	-0.6±8.2	3.33	<0.005
	"Minimal" + "declining"		20.3±1.8	12.3±5.0	-8.1±6.2		
Depression	"Progressive rise" + "sustained"	34	17.8±6.5	14.7±6.5	-3.1±7.4	1.46	<0.10
	"Minimal" + "declining"		21.5±7.4	14.6±6.5	-6.9±9.4		

* Mean±standard deviation, in micrograms per 100 cc.

† By subject-occasions we mean a single day on which a subject was tested, e. g., Subject A on Stress Day 1.

‡ On the basis of a single-tailed test.

sible to inquire into this relationship further by examining the extent of relationship between these two variables within each occasion. In order to determine the "within-occasion" relationship, the coefficients of correlation between the change in affect and the change in hormone level were determined for the day of each subject's greatest, median, and least increases in affect (Table 6). The correlation coefficient became increasingly positive and significant for each affect as the degree of affect change increased. The improvement in correlation was due to a real increase in correlatedness (covariance) rather than to an apparent increase resulting from alteration in variance, since the variances were found by Bartlett's test to be homogeneous. These data indicate that the relationship between affect change and hormone change occurred between the subjects on occasions of high increase in affect as well as between occasions. It is possible to represent this dual relationship schematically, as shown in Figure 2.

TABLE 6.—Intercorrelations (*r*) of Individual Change Scores for Plasma Hydrocortisone Level with Changes in Affect Rating *

Occasion	Correlation Coefficient (<i>r</i>) †			
	Anxiety	Anger	Depression	Combined Affect
Day of greatest increase in affect	0.396	0.334	0.231	0.222
Day of median increase in affect	0.326	0.298	0.042	0.138
Day of least increase in affect	-0.059	-0.007	-0.115	-0.042

* Both change scores for the Post minus Pre period.

† For 15 degrees of freedom and a *P* value equal to or better than 0.10; *r* ≤ 0.412.

Change in Hydrocortisone Level in Relation to Quality of Emotional Response.—The evidence presented so far has indicated that a relative increase in the plasma level of hydrocortisone occurs in response to intense emotional experiences irrespective of the nature of the emotion experienced. Attempts to ascertain whether a specific affect, such as anxiety, produced a greater hormone change than anger or depression were negative. In order to explore more fully the possibility that the quality of emotion experienced by the subject may influence the extent of adrenocortical activation, one affect (anxiety) was studied in greater detail. This particular affect was chosen because it is

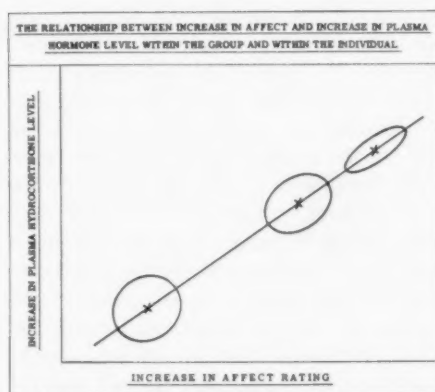


Fig. 2.—A schematized diagram of the relationship between the increase in affect rating and the increase in the plasma level of hydrocortisone. The group means are given by the crosses, while the scatter of the individual values are represented by the ellipses. The principal axis of each ellipse gives the variance for the group and is of the same magnitude for each ellipse; the minor axis indicates the degree of correlation of the two variables. With increasing affect, the eccentricity of the ellipses increases.

better understood than anger or depression, and because it constitutes the core problem in the etiology of the psychoneuroses. Since anxiety is a final common response to a variety of disturbing stimuli, we decided to examine the changes in hydrocortisone level as a function of the sources of the anxiety exhibited. Elsewhere¹⁰ we have indicated that anxiety may derive from feelings of shame, guilt, and/or disintegration (ego dissolution). By "disintegrative anxiety" we imply that the patient fears that his mental illness may be severer than had previously been apparent, that he may lose control of himself and behave in a totally unacceptable way, that he may lose contact with the environment, or that he may become insane. The patients were considered to be experiencing disintegrative anxiety if they verbalized such a fear during the experimental procedure in such a way as to indicate that this was more than a fleeting thought. Out of 54 subject-occasions on which a stress interview was conducted, 10 resulted in the appearance of disintegrative anxiety, while during the remaining 44 anxiety was evidenced without a detectable disintegrative quality (nondisintegrative) (Table 7). The occurrence of an absolute increase in the plasma level of hydrocortisone following the stress interview has been shown previously¹⁰ to represent a considerable stimulation of the adrenal cortex. When such an estimate was chosen as an index of response, it was found that an absolute increase from the *pre* to the *post* periods, as well as from the *pre* to the *extra* periods, occurred more frequently in those instances when dis-

integrative anxiety was manifested. This result is highly significant at the 0.05 level.

The question may be raised whether this result was simply a function of the anxiety level. That is, were the people who were categorized as manifesting disintegrative anxiety simply persons with higher anxiety ratings, and, if so, were these high levels the basic factor associated with the absolute increase in hydrocortisone level? In order to determine whether disintegrative anxiety per se provided a particular powerful stimulus to the pituitary-adrenal system irrespective of the momentary anxiety rating, a group of 10 subject-occasions during which no disintegrative anxiety was detected were compared with the 10 subject-occasions of Table 7 on which disintegrative anxiety occurred. These 10 nondisintegrative patient-occasions were matched as closely as possible with respect to (a) anxiety level, as obtained from the ratings, and (b) anxiety pattern throughout the day (i. e., transient, sustained, etc.). Insofar as possible, an attempt was made to have the same people represented in each column, that is, to pick out for a given patient two occasions which were similar with respect to anxiety level and pattern but which differed in that one was disintegrative and one was not. It was possible to find such relatively precise matching on only 4 of the 10 occasions. It is particularly interesting that all four of these patients showed a greater *pre* to *post* hydrocortisone decrease on the nondisintegrative occasions than on the disintegrative ones. The 10 subject-occasions on which disintegrative anxiety occurred included 6 during which an absolute increase in plasma hydrocortisone level occurred, while none occurred on the nondisintegrative occasions. This is significant at the 0.005 level. This analysis strongly suggests that the relationship between disintegrative anxiety and hormone level is not simply a function of the intensity of the anxiety experienced but that the special qualities of the disintegrative experience exert a prepotent effect on the pituitary-adrenal system.

TABLE 7.—Frequency of Absolute Change in Level of Plasma Hydrocortisone as a Function of the Quality of Anxiety Experienced in the Stress Interviews

Quality of Anxiety Experienced in Interview	Absolute Change (Post-Pre) in Plasma Hydrocortisone Level		Absolute Change (Extra-Pre) in Plasma Hydrocortisone Level	
	Increase	Decrease	Increase	Decrease
Disintegrative	6	4	4	6
Nondisintegrative	10	34	3	41
	$\chi^2=3.90$ $P<0.05$		$\chi^2=5.28$ $P<0.025$	

Additional confirmation is derived from an analysis of plasma hydrocortisone levels of eight physically healthy anxious patients utilized in other experiments. They manifested a plasma hydrocortisone level above the upper 0.05 limit of confidence of a larger group of 32 anxious patients from which they were drawn (above $30\mu\text{g. per } 100\text{ cc.}$). Three of these subjects were withdrawn from the study before completion of the experiment because of actively proceeding personality disintegration associated with a high degree of emotional disturbance. One of them achieved a hydrocortisone level of $62.5\mu\text{g. per } 100\text{ cc.}$; another maintained a level 200% higher than the control group on two days, and the third, 300% above normal controls. All three manifested disintegrative anxiety. Furthermore, six out of the eight subjects whose 9:00 a. m. plasma hydrocortisone levels were among the highest showed severe disintegrative anxiety. This was in contrast with the nondisintegrative anxiety in the patients at the low end of the plasma hydrocortisone distribution.

The extremely high plasma hydrocortisone levels present in patients with disintegrative anxiety do not in themselves establish the fact that the rate of adrenocortical hormone production in these same persons is comparably great. However, since anxious patients clear hydrocortisone at a significantly faster rate from plasma, the ability to maintain the high plasma level seen in the eight subjects of this study suggest that the rate of adrenocortical hormone production may be several times as great as normal, and perhaps approaching maximal output.¹⁷

Change in Hydrocortisone Level in Relation to Behavior of the Stresser.—In the two preceding sections on results, the relation of psychological response to the stress stimulus (i. e., the stress interview) and the change in plasma hydrocortisone level has been explored in considerable detail. In the present section, we propose to examine the relation between the stress stimulus and the hormone level change. On the assumption that the psychological stimulus of the

stress interview included the total behavior of the stresser, as well as the actual content of the stress interview, a number of questions arose: Was the behavior of the stresser related to subsequent changes in hydrocortisone level? If the stresser conducted the interview in a particular way, was he more likely to produce an increase in hydrocortisone level in the subject than if he conducted the interview in another way? One factor of special significance in this connection was the attitude of the stress interviewer toward the subject. For each subject studied we selected the day on which the stresser's attitude toward the subject was most positive and the day on which it was most negative. By positive attitude we mean behavior on the part of the stresser which conveyed to the observers a sense of friendliness and respect, whereas by negative attitude we mean behavior on the part of the stresser which conveyed to the observers a sense of unfriendliness and depreciation. For many patients the difference between these two contrasting occasions was quite small, since the stresser's attitude tended to be fairly consistent toward a given patient. In addition, the stresser usually avoided sharply negative attitudes out of therapeutic considerations. When the mean change in hydrocortisone level which occurred on the day that the stresser manifested his most positive attitude toward the subject was compared with the mean change on his most negative day, the difference in change scores tended toward statistical significance, but fell short of the conventional 0.05 level of confidence. Nevertheless, a distinct tendency was observed for plasma hydrocortisone to show a less than usual diurnal decline on the days of most negative attitude (Table 8).

The importance of the behavior of the stress interviewer also emerged in an analysis of the day-by-day responses of those subjects who completed the entire four-day experiment. Elsewhere we shall report that the plasma hydrocortisone level, the stress response in a perceptual decision task, and the affect rating for anger were increased

STRESSFUL INTERVIEW—EMOTIONAL RESPONSES AND PLASMA HYDROCORTISONE

TABLE 8.—*Relation of the Stress Interviewer's Attitude Toward the Experimental Subject to the Change in Plasma Hydrocortisone Level (Post Minus Pre)*

Occasion	No. of Occasions	Plasma Hydrocortisone Level *			t	P †
		Pre	Post	Change		
Day of most positive attitude	16	21.0±6.7	13.7±4.5	-7.3±7.5	1.71	<0.10
Day of most negative attitude	16	19.1±6.6	15.4±7.7	-3.7±9.3		

* Mean±standard deviation, in micrograms per 100 cc.

† On the basis of a single-tailed test.

to a greater extent following the stress interview on the second day than on either of the other two experimental days. This finding became more understandable when viewed in relation to the behavior of the stresser. While many exceptions occurred, the stresser generally spent the first day's interview in getting acquainted with the patient and scanning for emotional problems of greatest current relevance in a way quite analogous to that employed in psychotherapy. On the second day, he generally made a particularly vigorous and persistent effort to evoke a striking emotional response through exploration of conflictual content and frequently by means of a negative attitude. By Day 3, the exploration of conflictual content continued in much the same way as on Day 2, but the stresser's attitude tended to ease, particularly toward the end of the stress interview, since this was the last day of the experiment and the research group wanted to see some constructive carry-over into the patient's own therapy. In other words, the social context of the

TABLE 9.—*Frequency of Stresser's Most Positive and Most Negative Attitudes on Stress Interview Days*

Attitude of Stresser	Stress Interview Days		
	Day 1	Day 2	Day 3
Most negative attitude	4	8	7
Most positive attitude	10	3	6
		$\chi^2=4.92$	
		$P<0.10$	

experiment seemed to favor a maximization of the stressful stimulus, especially in anger, of the stressful stimulus on the second S. I. day. When the distribution of positive and negative attitudes is viewed on a day-by-day basis, the second S. I. day stands out as having the greatest frequency of negative attitudes on the part of the stresser (Table 9). The stresser exerted the most urgent pressure on the subjects, particularly through the development of unfriendly, depreciating attitudes on the second S. I. day; the subjects responded with a striking emotion in anxiety and depression as well, and the hydrocortisone levels declined considerably less than on the other S. I. days, maintaining an elevated level throughout the morning.

As an additional index of the behavior of the stresser, the stresser estimated the strength of the psychological stimulus which he had applied to the subject, taking into account the content of the interview, his own attitude, and the nature of the communication between the patient and himself. This estimate was originally intended to be a total stimulus estimate, but it soon became apparent that the estimate was contaminated by feedback from the patient about the nature of his response to the psycho-

TABLE 10.—*Change in Plasma Hydrocortisone Level Following a Stress Interview Administered to Each of Seventeen Anxious Patients on Three Consecutive Days*

Occasion	Plasma Hydrocortisone Level *		
	Pre	Post	Change
Day of greatest stimulus intensity	19.4±5.8	14.6±7.7	-4.8±8.0
Day of median stimulus intensity	17.9±6.1	15.7±5.4	-2.3±8.6
Day of least stimulus intensity	21.2±7.9	14.0±5.4	-7.1±8.9

* Mean±standard deviation, in micrograms per 100 cc.

TABLE 11.—*Analysis of Variance Among Changes in Plasma Hydrocortisone Level (Post Minus Pre) for Various Degrees of Stimulus Intensity*

Source of Variation	df	Mean Square	F	P
Between subjects	16	77.11	1.49	Not sig.
Between degrees of stimulus intensity	2	101.62	1.97	>0.10
Linear	(1)	46.36	0.89	Not sig.
Quadratic	(1)	156.88	3.04	<0.10
Error	32	51.59		
Total	50			

logical stimuli. Nevertheless, the rating was primarily formulated in stimulus terms, and was recognized as a necessarily rough estimate. For each patient, the stimulus-intensity ratings were ranked as follows: day of greatest intensity, day of median intensity, and day of least intensity.

When the change scores on these days for plasma hydrocortisone level were examined by means of an analysis of variance, a tendency toward relationship between stimulus intensity and change in plasma level occurred short of the conventional 0.05 level of significance. Since the hormone change on the day of greatest stimulus intensity is about midway between the hormone changes of the other two days, the quadratic term is more significant than the linear term. This result was surprising, since a linear relationship had been tentatively assumed on the basis of the affect response-steroid results previously obtained. While the stimulus-intensity rating was a rough estimate as compared with the affect ratings obtained by the observers and its lack of delineation might have accounted for the unexpected shape of the relationship, another explanation appears somewhat more probable. It had been our original intent¹² to increase the stimulus intensity progressively over the three stress interview days, and the stresser actually rated the day of greatest stimulus intensity as Day 3 most frequently (11 out of 17 possible), the day of median stimulus intensity as Day 2 most frequently (10 out of 17), and the day of least stimulus intensity as Day 1 most frequently (10 out of 17). From the preceding data we know that the affective response of the patients was greatest on Day 2, even though the stresser considered his stimulus to be stronger on Day 3. The stresser was unable to differentiate the stimulus intensity sufficiently between Days 2 and 3. This could account for a quadratic relationship. This relationship was less impressive than that occurring between change in hormone level and emotional response. It seems that defining the relationship between psychological stress and

adrenocortical activity in terms of emotional responses leads to more significant relationship than when defined in terms of stimulus conditions. Stimulus conditions are important mainly insofar as they evoke certain emotional responses. If they do not evoke these responses, the chances of their being associated with abnormally high hormone levels are reduced.

Comment

This study gave a series of indications that there is a significant association between emotional response to psychological stress and change in plasma hydrocortisone level. While the relationships reported are, for the most part, not extreme or dramatic, they are quite consistent when viewed from various angles and are reasonably impressive—particularly in view of the fact that we are mainly dealing with low-order emotional responses. By the nature of the experiment, subjects could participate in it only if their degree of emotional disturbance was of mild or moderate severity. When one considers the full range of emotional experience encompassed by the terms anxiety, anger, and depression (as defined earlier), it is evident that subjects at the higher end of the scale could not remain sufficiently quiet and cooperative for several hours on four consecutive days to permit completion of the required tasks. For example, no patient completed the experiment who was experiencing panic, violent rage, or suicidal depression. In fact, such experiences are virtually absent from our behavioral observations, even on a transitory basis. This is largely a function of the fact that such patients were deliberately avoided in selection. A few who showed such characteristics early in the experiment were withdrawn before completion because it was felt that the procedure jeopardized their therapeutic needs. The stresser, and likewise the other members of the research group, were considerably influenced by their training and experience in treatment of patients. Furthermore, the experiment took place in an intensive treatment hospital,

where there are always many factors operating to relieve patients' distress. Taking all these considerations into account, it becomes quite understandable why the vast majority of the affect ratings were in the lower half of the rating scale; this was true of anxiety, anger, and depression. These affect levels were well below the original expectations of the research group.

In view of this fairly narrow range of emotional variation, it is noteworthy that the affect-steroid relationship emerged as regularly as it did. The fragments of data available from this and other studies^{8,11,18} suggest that this relationship probably becomes more striking as higher levels of emotional disturbance are reached. In the present study, the correlation between the hormone level and the affect rating occurring on the day of greatest increase in affect and the consistently high hormone levels which were present in the patients with disintegrative anxiety strongly support this thesis. These data suggest that the highest levels and/or increases in hydrocortisone occur (a) with a sharp increase in emotional distress, (b) with prolonged high levels of emotional distress, and/or (c) with thoughts which imply that a profound threat to the organism is in the offing, whether or not the immediate distress is very great (e. g., disintegrative anxiety). In other words, the greatest adrenocortical responses seem to occur when the patient's psychological position is one which borders on desperation, with respect either to the immediate present or to the near future.

While we attempted to relate individual affects to the change in hormone level, it was recognized that these affects were not independent, but, rather, were a set of interrelated variables. A number of alternative conclusions may be drawn about the meaning of the relationship between affect change and hormone change: (1) Our ratings did not really differentiate among the affects as well as we should have liked, and hence we were calling the same thing by different names; (2) our ratings did differentiate, but all the

affects were increased by the stress interview in a parallel fashion, or (3) the stress interview produced an undifferentiated affective arousal, and the change in hormone level is related only to such an undifferentiated affective arousal. The present study did not fully differentiate among these possibilities, and it remains for future investigations to examine these alternatives more carefully. However, it should be noted that difficult circumstances tend to evoke a wide variety of feelings in each person. When injured, we tend to feel anxious *and* depressed *and* angry, in varying mixtures and configurations. Although highly individual factors influence the emotional outcome of a stressful situation, clinical experience suggests that a single affect rarely occurs in pure form.

The evidence presented here, when coupled with the data of others cited at the beginning of this paper, strongly indicates that emotional disturbance in man is associated with increased adrenocortical production. This increase in activity is associated with a wide variety of stressful conditions and emotional responses. In this respect, the adrenocortical response which occurred is quite analogous to that observed following various kinds of physical stresses; i. e., a wide variety of noxious agents may trigger the adrenal response. On a rather high level of abstraction, it may be said that these physical stresses have something in common: a threat to the survival of the organism. This concept carries over to the psychological stresses but must be broadened to include the individual's essential values. The present study has indicated that increased adrenocortical activity may be associated with stresses which do not threaten the physical survival of the subject but do threaten his self-respect or his social status. It might be useful in human stress research to broaden the "threat to survival" concept to one which becomes "threat to survival as a self-respecting, socially functioning human being."

The multiplicity of relationships demonstrated in this report between various psychological parameters and the change in hormone level may simply represent opposite sides of the same coin. This is particularly true for the relationships of psychological stimulus and response variables to steroid change. It has been pointed out previously that stimulus factors affect hormone level only when the stimulus is meaningful to the subject, i. e., when the psychological stimulus produces a psychological response. Thus, the negative attitude of the stresser and the affective arousal in the patients are certainly not unique variables. Nevertheless, the value of presenting analyses relating both of these parameters to plasma hydrocortisone change serves to elaborate the stimulus-response character of psychological stress and consequently brings the concept of psychological stress into harmony with other forms of biological stress so that the phenomenon is understood in terms of the original meaning of a stimulus-response process.

Although a wide variety of psychological responses were capable of arousing the secretion of hydrocortisone, at least one specific response exerted an especially strong influence. The occurrence of disintegrative anxiety following the stress interview was demonstrated to be associated with greater increases in plasma hydrocortisone level than the occurrence of nondisintegrative anxiety (shame and/or guilt) even when the ratings for anxiety experienced were identical. We have shown that patients with disintegrative anxiety manifest much higher plasma levels of hydrocortisone than patients whose anxiety stems from feelings of shame or guilt. It may well be that our rating scale for anxiety does not correctly assess the quantity of anxiety present in the patient experiencing ego dissolution, but further information on this point must await future investigation.

Summary

The present report has attempted to investigate the relationship between emotional

response and the plasma level of hydrocortisone under the impact of a stressful interview. Two major areas of psychological-endocrine interaction were examined: (1) the effect of emotional response and (2) the effect of the psychological stimulus on the change in the hormone level. The degrees of increase in anxiety, anger, depression, and a combined affect rating were found to be significantly and linearly related to the change in the plasma hydrocortisone level. This relationship was maintained even though the affect change was rated for only a short time period. It would appear that the plasma level of hydrocortisone is increased by any type of emotional arousal. However, data were presented which indicated a particularly striking effect when anxiety of a disintegrative nature was developed in the course of the stress interview. Stimulus-hormone relationships were also found to occur, but these relations were generally less striking than response-hormone relations. The stresser's attitude and his total stimulus intensity rating tended to parallel the change in plasma hormone level. A significant stimulus-hormone relationship occurred when the stimulus produced a relatively intense emotional response in the subject. The findings presented are of special interest because this experiment included only a moderate range of emotional responses. The limited data available on more extreme responses suggest that an even greater degree of adrenocortical activation occurs.

Dr. David McK. Rioch made several stimulating suggestions concerning the data analysis. Miss Betty Lou Day and Mrs. Judith Kandler assisted in conducting the statistical analyses.

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REFERENCES

1. Frost, J. W.; Dryer, R. L., and Kohlstaedt, K. G.: Stress Studies on Auto Race Drivers, *J. Lab. & Clin. Med.* 38:523-525, 1951.
2. Hill, S. R., Jr.; Goetz, F. C.; Fox, H. M.; Murawski, B. J.; Krakauer, L. J.; Reifstein, R. W.; Gray, S. J.; Reddy, W. J.; Hedberg, S. E.; St. Marc, J. R., and Thorn, G. W.: Studies on

- Adrenocortical and Psychological Response to Stress in Man, A. M. A. Arch. Int. Med. 97:269-298, 1956.
3. Persky, H.: Response to a Life Stress: Evaluation of Some Biochemical Indices, J. Appl. Physiol. 6:369-374, 1953.
4. Dreyfuss, F., and Feldman, S.: Eosinopenia Induced by Emotional Stress, Acta med. scandinav. 144:107-113, 1952.
5. Humphreys, R. J., and Raab, W.: Response of Circulating Eosinophils to Nor-Epinephrine, Epinephrine and Emotional Stress in Humans, Proc. Soc. Exper. Biol. & Med. 74: 302-303, 1950.
6. Pincus, G., and Hoagland, H.: Adrenal Cortical Responses to Stress in Normal Men and in Those with Personality Disorders: II. Analysis of the Pituitary-Adrenal Mechanism in Man, Am. J. Psychiat. 106:651-659, 1950.
7. Bliss, E. L.; Migeon, C. J.; Branch, C. H. H., and Samuels, L. T.: Reaction of the Adrenal Cortex to Emotional Stress, Psychosom. Med. 18: 56-76, 1956.
8. Board, F.; Persky, H., and Hamburg, D. A.: Psychological Stress and Endocrine Functions: Blood Levels of Adrenocortical and Thyroid Hormones in Acutely Disturbed Patients, Psychosom. Med. 18:324-333, 1956.
9. Hetzel, B. S.; Schottstaedt, W. W.; Grace, W. J., and Wolff, H. G.: Changes in Urinary 17-Hydroxycorticosteroid Excretion During Stressful Life Experiences in Man, J. Clin. Endocrinol. 15: 1057-1068, 1955.
10. Persky, H.; Grinker, R. R.; Hamburg, D. A.; Sabshin, M.; Korchin, S. J.; Basowitz, H., and Chevalier, J. A.: Adrenal Cortical Function in Anxious Human Subjects: Plasma Level and Urinary Excretion of Hydrocortisone, A. M. A. Arch. Neurol. & Psychiat. 76:549-558, 1956.
11. Price, D. B.; Thaler, M., and Mason, J. W.: Preoperative Emotional States and Adrenal Cortical Activity: Studies on Cardiac and Pulmonary Surgery Patients, A. M. A. Arch. Neurol. & Psychiat. 77:646-656, 1957.
12. Grinker, R. R.; Korchin, S. J.; Basowitz, H.; Hamburg, D. A.; Sabshin, M.; Persky, H.; Chevalier, J. A., and Board, F. A.: A Theoretical and Experimental Approach to Problems of Anxiety, A. M. A. Arch. Neurol. & Psychiat. 76: 420-431, 1956.
13. Hamburg, D. A.; Sabshin, M.; Board, F. A.; Grinker, R. R.; Korchin, S. J.; Basowitz, H., and Chevalier, J. A.: Classification and Rating of Emotional Experiences, A. M. A. Arch. Neurol. & Psychiat. 79:415-426, 1958.
14. Persky, H.: Adrenocortical Function in Anxious Human Subjects: Disappearance of Hydrocortisone from Plasma and Its Metabolic Fate, J. Clin. Endocrinol. 17:760-765, 1957.
15. Persky, H.: Adrenal Cortical Function in Anxious Human Subjects: Effect of Corticotropin on Plasma Hydrocortisone Level and Urinary Hydroxycorticoid Excretion, A. M. A. Arch. Neurol. & Psychiat. 78:95-100, 1957.
16. Grinker, R. R.; Sabshin, M.; Hamburg, D. A.; Board, F. A.; Basowitz, H.; Korchin, S. J.; Persky, H., and Chevalier, J. A.: The Use of an Anxiety-Producing Interview and Its Meaning to the Subject, A. M. A. Arch. Neurol. & Psychiat. 77:406-419, 1957.
17. Peterson, R. E., and Wyngaarden, J. B.: The Miscible Pool and Turnover Rate of Hydrocortisone in Man, J. Clin. Invest. 35:552-561, 1956.
18. Board, F.; Wadson, R., and Persky, H.: Depressive Affect and Endocrine Functions: Blood Levels of Adrenal Cortex and Thyroid Hormones in Patients Suffering from Depressive Reactions, A. M. A. Arch. Neurol. & Psychiat. 78:612-620, 1957.

Psychiatrists' Conceptions of the Schizophrenogenic Parent

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The efforts of some hardy pioneers in establishing the psychotherapy of schizophrenia as a reasonable procedure have led to a geometric increase in interest in this topic during the past 10 years. Possibly as a consequence of therapists' running head-long into the family of the schizophrenic, there has been an upsurge of interest in the problem of the "schizophrenogenic" parent. When one considers the size of the known and of the hospitalized schizophrenic population, and the countless encounters that must have occurred between psychiatrists and the parents of schizophrenics in the past 50 years, it is somewhat perplexing to discover that as a topic the parents have remained immune to scientific scrutiny until relatively recently. Even today, the reports on the family of the schizophrenic are largely impressionistic, and often unspecified as to size or bias of sample. An exception is the recent work of Lidz, at Yale University School of Medicine.

As we attempt to compare the various clinical descriptions of schizophrenogenic parents, it becomes intuitively obvious that some fundamental similarities exist among these separately offered conceptions. Typically, the mother of the autistic child is portrayed in such terms as "rejecting," "rigid," "perfectionistic," "anxious," "cold," and so

on, but these characterizations tend to be offered in a general and categorical way. Certainly, there exist parents with personality characteristics essentially similar to those of the schizophrenogenic parents but whose children are not schizophrenic. The existence of these "false-positives" poses a profound problem for theory.

It may be, however, that the problem is a false one, generated by a certain summariness of communication. The descriptions in the literature appear to have focused upon a few high lights in the personality picture, excluding the background, which can give depth and organization to the abstractions. For example, instead of employing the deceptively convenient label "the rejecting mother," we should attempt to understand the setting in which rejection appears to be so paramount a feature. What are the techniques of rejection? * How do these techniques qualify the impact and resultant of the rejection? What are the long-term and short-term origins of this particular interpersonal mode in this particular mother? Are other alternatives psychologically possible for the mother, or do they involve excessive anxiety? Does the child possess some special significance for the parent, or is the child an unfortunate by-product of the pathogenic parent?

* Even the use of the term "rejection" introduces certain problems in clarification. It is an active term, one easily associated with hostility and one that gives rise to a private picture of what the mother would have to be like in order to be rejecting. Recently it has been postulated that the mother's "rejection" is at the meta-communicative level and consists of prohibiting the child from commenting on the nature of his relationship to her.*

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These are some of the obvious questions that arise in attempting to deal with the problem of the schizophrenogenic parent. A comprehensive, multidimensional description of personalities and their interactional significance is required to give greater meaning to the term "schizophrenogenic parent"; however, a thorny methodological obstacle must be overcome before this greater comprehensiveness of portrayal can be achieved.

A prime difficulty with the descriptions offered in the literature is that they are not readily comparable. The reader finds it simply impossible to assess the extent of equivalence or divergence among the characterizations offered. Language and concepts are so individually employed as to make comparisons or formulations an impossible endeavor.

If we are to benefit from the experience embodied in the various impressions of pathogenic parents, it is necessary to be able objectively to compare and contrast what has been said. The agreements must be noted and weighed, for the agreement of widely separate observers is presumptive evidence for the validity of their observations. Differences must be evaluated, too, for they suggest error or the necessity of a more complex understanding of a phenomenon.

Not only are there problems of divergence among observers, but the individual observer faces some obvious problems that immediately arise in considering the validity of his clinical descriptions of the parents of schizophrenics.

1. How much does the observer's bias in favor of his patient influence his picture of the parent or parents?

2. Is there a difference in the personality structures of parents of schizophrenics of different nosological types? Are there differences between the parents of the schizophrenic with an onset in late adolescence and the parents of the childhood schizophrenic?

3. It is extremely rare in the literature for there to be data concerning the intensive study of a parent of a schizophrenic. Sper-

ling describes one such mother whom she treated along with the child.⁵ We can find no descriptions of the intensive psychotherapy of the father of a schizophrenic in the literature. Is there something about the family constellation and the parental interaction that makes the couch off limits for the parent of the schizophrenic? If so, it would tend to support the hypothesis proffered by some that the psychosis of the child is important in the family's mental economy. Is the psychiatrist's view of the mother, then, (and to a less extent of the father) partially a product of his unconsciously sensing the extreme anxiety of the parent and the shakiness of the entire family structure? Has this fear of upsetting the family homeostasis been a factor in the paucity of intensive clinical study of the parents of schizophrenics?^{8,9,10}

Such questions are but a few of the many complex variables that enter into the clinician's impressions of the parents of schizophrenics, and, because there is a paucity of material on the topic, we felt that it might be profitable to obtain the clinical descriptions of the parents of schizophrenics from a number of therapists who had worked intensively with schizophrenic patients in long-term psychotherapy and, preferably, who had had psychotherapeutic experience with the parents of schizophrenics as an outgrowth of collaborative or conjoint therapy.

The Q-sort procedure* was felt to be ideal for this type of description, since by means of a forced sort the clinicians would be restricted to an expression of their impressions that would be comparable from person to person and, in addition, would retain an equal status for descriptions of the father and of the mother. As mentioned above, it is obvious from the literature that there are many more words written about the mother than the father.

The sorters were asked to describe either a hypothetical family of a schizophrenic child

* The Q Deck used may be obtained from the Palo Alto Medical Research Foundation.

or adult or a real family which they considered representative. The inclusion of the parents of schizophrenic children with the parents of the late adolescent and adult schizophrenics was deliberate, for, although we feel there may be real differences in personality structure between the two groups of parents, it would be interesting to see how comparable the descriptions appeared when Q-sorted and what the outstanding similarities and differences might be. Examination of the data, interestingly enough, reveals that the clusters were not determined by whether the parents being described were those of schizophrenic children or of older schizophrenics. It was further interesting to us that the sorters did not cluster according to similarity of training and geographical locations. Some sorters who were actually working together in the same institution described parents who fell in different clusters.

The various descriptions of schizophrenic parents provided by the participating psychiatrists were compared with the descriptions characterizing a group of parents of autistic children studied by a quite different methodology,³ thus providing a limited test of the validity of the several clinical impressions.

Contact was made with a number of psychiatrists who had a special interest in the nature and origins of childhood or adolescent schizophrenia, and they were asked to express by means of the Q-sort method their conceptions of both the schizophrenic "mother" and the schizophrenic "father." Twenty psychiatrists provided sorts of the hypothesized mother, while eighteen completed sortings of the hypothetical father. Cooperating psychiatrists who subscribed to the existence of several kinds of schizophrenogenic parents were instructed to describe one particular type. This approach was adopted in order to eliminate the averaging distortion that otherwise would have occurred from an attempt to force one general, over-all description to encompass the various subtypes. The psychiatrists ap-

peared to be describing a dyad, rather than a particular mother and an unrelated special father. From statements that a number of the sorters sent with their Q-sorts, it was apparent that they varied in the relative assessment of malignancy of the two parents.

The Q-sort method is in essence a rating scheme wherein a judge, the clinician, evaluates a large number of personality-relevant statements and ranks them in terms of their judged salience for the person under consideration. Usually, the items are placed in nine or more piles, ranging from those considered most salient to those considered least salient for the subject. The method has been discussed and justified elsewhere.^{2,5} Such an item as "is a hostile person" may by its placement be the most behaviorally relevant aspect of the person under consideration, or, on the contrary, may appear not applicable to this subject. In order to construct appropriate and relevant statements for the Q-items, the help of some 25 psychiatrists and psychologists was sought, and the 108 items underwent several revisions in pretests before being fixed in the form used in this study.

The items employed were continuistic in nature, pathology being expressed by the extremeness of an item placement or by the suitable conjunction of several items. Emphasis was laid on being able to express the distinction between manifest and latent aspects of behavior. The final 108 items were felt by us to be capable of a rather complex evaluation of a patient and the functional properties of his personality system. However, it should be noted that several of the participating psychiatrists found the Q-set inadequate and the sorting procedure unduly constraining. Whether this reaction reflects an inadequacy of the technique or an uneasiness on the part of some participants with the sort of theoretical commitments required by the procedure it is difficult to say. In any event, the results to be reported here should be recognized as limited by the particular methodology employed.

SCHIZOPHRENOGENIC PARENT-PSYCHIATRISTS' CONCEPTIONS

TABLE 1.—Intercorrelations Among Q-Sorts of the Schizophrenogenic Mother

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1																				
2	0.39																			
3	0.54	0.40																		
4	0.34	0.15	0.51																	
5	0.34	0.25	0.24	0.28																
6	0.47	0.32	0.71	0.43	0.26															
7	0.00	0.10	0.03	0.12	0.09	-0.11														
8	0.12	0.02	0.18	0.12	0.11	0.27	0.01													
9	0.44	0.17	0.51	0.38	0.32	0.49	0.08	0.27												
10	0.38	0.30	0.58	0.50	0.27	0.50	0.12	0.19	0.42											
11	0.46	0.48	0.55	0.45	0.29	0.64	-0.11	0.19	0.51	0.52										
12	0.46	0.23	0.72	0.54	0.16	0.66	-0.11	0.05	0.50	0.54	0.66									
13	0.31	0.40	0.43	0.34	0.34	0.44	0.18	0.14	0.44	0.44	0.47	0.40								
14	0.28	0.22	0.36	0.23	0.21	0.42	0.06	0.34	0.40	0.33	0.43	0.39	0.41							
15	0.12	0.28	0.15	0.06	0.30	0.31	-0.06	0.41	0.30	0.20	0.22	0.14	0.42	0.51						
16	0.35	0.24	0.41	0.47	0.11	0.30	-0.11	0.26	0.31	0.47	0.45	0.15	0.04	-0.61						
17	0.41	0.34	0.57	0.43	0.13	0.48	0.00	-0.01	0.38	0.38	0.54	0.55	0.29	0.15	-0.14					
18	0.28	0.37	0.47	0.28	0.14	0.47	-0.05	0.16	0.32	0.37	0.37	0.46	0.30	0.44	0.31	0.22	0.21			
19	0.42	0.09	0.53	0.49	0.03	0.66	-0.07	0.02	0.03	0.42	0.58	0.61	0.34	0.12	-0.03	0.63	0.63	0.26		
20	0.22	0.36	0.25	0.11	0.34	0.15	0.06	0.03	0.36	0.36	0.43	0.25	0.42	0.15	0.11	0.22	0.34	-0.02	0.21	

0.30

TABLE 2.—Original and Rotated Factor Matrices—Schizophrenic Mother Data

Sorter	Original Factors				Rotated Factors			
	A*	B*	C*	h ²	A*	B*	C*	h ²
1	617	080	100	397	381	263	430	399
2	493	-141	173	293	121	313	425	293
3	813	215	-092	716	063	365	378	716
4	908	194	116	421	451	171	435	422
5	408	-267	240	295	-045	322	436	296
6	765	143	-330	715	673	487	157	715
7	037	-225	323	156	-263	041	298	160
8	262	-297	-303	249	055	487	-095	249
9	661	-119	021	452	293	459	394	452
10	692	-035	055	483	355	405	434	478
11	809	136	-022	673	578	387	437	675
12	747	295	-137	664	701	289	303	667
13	640	-173	093	616	114	552	446	517
14	538	-358	-340	533	183	707	034	534
15	369	-562	-340	568	-061	748	-058	567
16	495	449	167	475	549	-092	406	475
17	619	436	198	612	601	-024	503	615
18	514	-053	-332	377	387	477	019	378
19	028	393	-069	751	819	-016	283	751
20	429	-171	401	374	-024	200	577	374

TABLE 3.—Original and Rotated Factor Matrices—Schizophrenogenic Father Data

Sorter	Original Factors				Rotated Factors			
	X*	Y*	Z*	h ²	X*	Y*	Z*	h ²
1	452	490	-230	497	095	627	307	496
2	426	-100	-232	245	433	242	019	246
3	679	-371	-162	625	781	102	078	626
4	-112	446	-113	224	-335	327	066	224
5	-183	079	288	123	-243	-208	141	122
6	649	-252	-292	570	709	258	028	570
7	426	049	039	185	291	150	278	184
8	230	383	-375	340	015	582	037	340
9	347	290	522	433	046	-110	647	433
10	631	133	306	509	348	092	618	511
11	741	226	334	712	371	170	739	713
12	672	-264	245	581	633	-109	412	582
13	422	337	243	351	075	196	555	352
16	542	-157	-016	319	515	094	211	319
17	759	-237	051	635	719	070	334	633
18	574	-315	535	715	533	-373	540	715
19	-158	-188	333	171	-072	-403	063	172
20	-337	-172	448	344	-240	-531	056	343

TABLE 4.—Intercorrelations Among Q-Sorts of the Schizophrenogenic Father

	1	2	3	4	5	6	7	8	9	10	11	12	13	16	17	18	19	20
1																		
2	0.22																	
3	0.17	0.48																
4	0.07	0.02	-0.16															
5	0.02	-0.10	-0.15	0.13														
6	0.37	0.34	0.60	-0.10	-0.16													
7	0.19	0.14	0.19	0.00	-0.21	0.21												
8	0.46	0.10	0.05	0.17	-0.14	0.17	0.08											
9	0.28	-0.03	0.19	0.00	0.17	0.11	0.22	-0.06										
10	0.29	0.19	0.42	0.06	0.07	0.34	0.25	0.06	0.36									
11	0.28	0.27	0.34	-0.02	-0.05	0.34	0.21	0.15	0.46	0.67								
12	0.07	0.26	0.43	-0.29	0.00	0.41	0.20	-0.02	0.28	0.49	0.51							
13	0.42	0.20	0.20	0.17	0.19	0.11	0.18	0.15	0.41	0.38	0.40	0.26						
16	0.25	0.19	0.44	-0.02	0.07	0.49	0.20	0.06	0.13	0.36	0.26	0.49	0.29					
17	0.22	0.29	0.62	-0.12	-0.22	0.57	0.41	-0.01	0.23	0.47	0.54	0.53	0.26	0.46				
18	-0.14	-0.11	0.43	-0.36	-0.03	0.27	0.24	-0.13	0.38	0.43	0.62	0.61	0.25	0.34	0.51			
19	-0.11	-0.18	-0.05	-0.05	0.29	0.07	-0.14	-0.12	0.22	0.10	-0.12	-0.01	-0.01	0.08	-0.06	0.09		
20	-0.21	-0.05	-0.14	-0.09	0.28	-0.29	-0.07	-0.31	0.14	-0.11	-0.27	-0.17	0.06	-0.20	-0.21	0.05	0.42	

0.16

Following the data collection, the 20 Q-sorts of the schizophrenogenic mother were intercorrelated by the product-moment method, and the resulting correlation matrix (Table 1) was factor-analyzed by Thurstone's centroid method.⁷ Factor analysis is a statistical procedure which extracts from a large, undifferentiated mass of relationships those fewer underlying dimensions which can generate (and hence "explain") the original data. Specifically, in the present context, factor analysis groups those conceptualizations of the schizophrenogenic mother which are similar, statistically discerning the typological dimensions underlying the various impressions.

Three factor-dimensions appeared to exhaust the variance in the mother matrix. The usual procedure of rotating toward a criterion of simple structure was followed. Table 2 presents the original and final factor matrices.

The same procedure of intercorrelation and factor analysis was followed with the 18 Q-sorts of the schizophrenogenic father. The resulting correlation and factor matrices may be seen in Tables 3 and 4. Again, three factors contained almost all the communality characterizing the intercorrelations of sorts of the schizophrenogenic father.

The psychological meaning of these statistical analyses and groupings is presented and discussed in the next section.

Results and Comment

Conceptualizations of the Schizophrenogenic Mother.—The factor analysis indicates that the 20 participating psychiatrists see three different personality syndromes as, separately or in some conjunction, characterizing the schizophrenogenic mother. Although some of the sorters (e.g., psychiatrist 15 or 19) consider just one of these syndromes as sufficiently defining of the mother of the autistic child, others (e.g., psychiatrist 10 or 11) believe some mixture of all three components is involved.

The meaning and content of these three syndromes are conveniently expressed by

constructing a Q-sort best representing each factor derived. Then, by contrasting a factor Q-sort with an average Q-sort compiled by summing the sortings of all 20 participants, the items placing differently in the two sorts may be seen to define the psychological nature of the syndrome. Because of the part-whole relationship of the factor and average Q-sorts, this comparison procedure is a conservative one, for the differences between the two sorts tend to be attenuated. In general, differences of two intervals between the item placements of factor and averaged sorts are reliable and may be interpreted.

Comparing the Factor-A Q-sort with the over-all-consensus Q-sort, the following statements emerge to delineate the nature of this particular conception of the schizophrenogenic mother.

Items Relatively Characteristic of the Factor-A Syndrome

Item No.

- 7 Favors conservative values in a variety of areas.
- 9 Is intolerant of ambiguity.
- 12 Tends to be self-defensive; anticipates being attacked and criticized.
- 24 Prides self on being "objective," rational.
- 25 Tends toward overcontrol of her needs and impulses; binds her tensions excessively; delays gratification unnecessarily.
- 31 Would be organized and adaptive when under stress or trauma.
- 63 Judges self and others in conventional terms, like "popularity," "the correct thing to do," social pressures, etc.
- 70 Behaves in an ethically consistent manner.
- 72 Concerned with own adequacy. (N. B.: This refers to a clinical judgment.)
- 78 Follows routine in living; is orderly.
- 107 Satisfied with her self; is not subjectively aware of self-concern. (N. B.: This refers to subjective satisfaction with self.)

Items Relatively Uncharacteristic of the Factor-A Syndrome

Item No.

- 23 Tends to transfer blame.
- 30 Gives up and withdraws where possible in the face of frustration and adversity.
- 33 Is nervous, tense in manner; trembles, sweats, or shows other manifest evidence of anxiety.

- 49 Is distrustful of people in general; questions their motivations.
- 50 Is unpredictable and changeable in her behavior and attitudes.
- 53 Her various needs tend toward relatively direct and uncontrolled expression; unable to delay gratification; acts out.
- 59 Is concerned with her own body and the adequacy of its physiological functioning; aware of her bodily functions.
- 66 Seeks and enjoys aesthetic and sensuous impressions.
- 67 Is self-indulgent.
- 69 Is sensitive to anything that can be construed as a demand.
- 98 Has conflicts about giving.

Comment: It is clear from the above set of items that certain psychiatrists conceive of the schizophrenogenic mother as an over-controlled, highly moral, and determined woman, who is attuned to the world as she has chosen to understand it. She is relatively uninterested in sensuous experience and has a sternly developed sense of responsibility. This mother appears to be an assured, stolid person who entertains no self-doubts. Ambiguities are resolved into more convenient dichotomies. Her world is organized in terms of prescriptions and proscriptions, and life is not viewed as a pleasurable venture. Subtlety, spontaneity, and self-indulgence hold no positive values and may even be denounced as evil. We may label this kind of woman as the "puritanical" mother.

The items defining the second conception of the schizophrenogenic mother were derived also by contrasting the Factor-B Q-sort with the over-all sort.

Items Relatively Characteristic of the Factor-B Syndrome

Item No.

- 10 Her anxiety and tension find outlet in bodily symptoms and dysfunction.
- 12 Tends to be self-defensive; anticipates being attacked and criticized.
- 19 Seeks reassurance from others; requires narcissistic supplies.
- 36 Is subtly negativistic; tends to undermine and sabotage.
- 39 Tends to be conciliatory in her interpersonal relationships; accepts and fosters compromises; tends to be appeasing.
- 47 Has a readiness to feel guilty.
- 74 Lets other people take advantage of her; allows exploitation.
- 75 Is suggestible; overly responsive to other people's evaluations rather than her own.
- 93 Is feminine in her style and manner of behavior. (N. B.: This reflects the femininity of behavior.)
- 102 Has hostility toward others.

Items Relatively Uncharacteristic of the Factor-B syndrome

Item No.

- 15 Is skilled in techniques of play, pretending, and humor.
- 31 Would be organized and adaptive when under stress or trauma.
- 52 Behaves in an assertive fashion.
- 60 Has insight into her own motives and behavior.
- 65 Is able to sense other person's feelings; is an intuitive, empathic person.
- 70 Behaves in an ethically consistent manner.
- 81 Is able to convey her personal feelings and inner thoughts.
- 85 Emphasizes communication through action and nonverbal behavior.
- 92 Has social poise and presence; appears socially at ease.
- 94 Expresses her hostilities directly.
- 95 Is generally counterphobic in her handling of fears, anxieties, and conflicts. (N. B.: Extreme placement of this toward uncharacteristic end of scale reflects a phobic reaction.)
- 96 Values her own independence and autonomy.
- 100 Does not vary roles; relates to everyone in the same way.
- 107 Satisfied with her self; is not subjectively aware of self-concern. (N. B.: This refers to subjective satisfaction.)

Comment: From these differentiating items, the B-mother appears as a weak, anxious, and confused person, lacking in a sense of personal integrity, and consequently buffeted about by the conflicting pressures impinging upon her. In this conception of the schizophrenogenic mother, she is seen as dissatisfied with her self and as expressively inarticulate. She capitulates to demands, albeit subtly attempting to undermine the victory she so easily allows. She is dependent upon others in many ways—for her gratifications, for her sense of personal value, and for decisiveness, where she can only vacillate. Her behavior suggests a yearning for the role of a child, where

she would be nurtured, protected, and loved without having to assume a responsibility for herself and for others. This type of woman earns the label of the "helpless" mother.

When the Factor C Q-sort is aligned with the over-all Q-sort, the following items appear to indicate the character of this third conception of the schizophrenogenic mother.

Items Relatively Characteristic of the Factor-C Syndrome:

- Item No.
- 24 Prides self on being "objective," rational.
 - 32 Seems to be aware of her social stimulus value.
 - 37 Is guileful and potentially deceitful.
 - 38 Is sarcastic; cynical.
 - 61 Creates and exploits dependency in people; gives, but with strings attached.
 - 62 Tends to be rebellious and nonconforming.
 - 71 Has high aspiration level for self; ambitious; wants to get ahead.
 - 95 Is generally counterphobic in her handling of fears, anxieties, and conflicts. (N. B.: Extreme placement of this toward uncharacteristic end of scale reflects a phobic reaction.)
 - 97 Has conflicts about receiving and being given to. (N. B.: If this item is placed toward uncharacteristic end of scale, it reflects the kind of person who "takes" excessively, seemingly without guilt or anxiety.)
 - 98 Has conflicts about giving.
 - 102 Has hostility toward others.
 - 103 Thinks and associates to ideas in unusual ways; has unconventional thought processes.

Items Relatively Uncharacteristic of the Factor-C Syndrome

- Item No.
- 1 Critical, not easily impressed, skeptical.
 - 5 Behaves in an indulgent and forgiving way.
 - 7 Favors conservative values in a variety of areas.
 - 17 Behaves in a sympathetic manner.
 - 26 Is efficient; gets things done.
 - 27 Is adequate in her sexual role.
 - 35 Has warmth; has the capacity for close relationships.
 - 39 Tends to be conciliatory in her interpersonal relationships; accepts and fosters compromises; tends to be appeasing.
 - 44 Is psychologically oriented and sophisticated; evaluates the motivation of others in interpreting situations.
 - 46 Behaves considerably toward others.

- 70 Behaves in an ethically consistent manner.
- 75 Is suggestible; overly responsive to other people's evaluations rather than her own.
- 77 Appears straightforward, forthright, candid in dealings with others.
- 83 Is genuinely sympathetic; compassionate for and with other people.
- 93 Is feminine in her style and manner of behavior. (N. B.: This reflects the femininity of behavior.)

Comment: This conception of the schizophrenogenic mother introduces quite a different dimension from those encompassing the A- and B-mother types, previously described. The C-mother is seen as coolly, perceptively guileful and manipulative. Rebelliousness, but not impulsivity, is present. She is a highly driven person, who is devious, hostile, unforgiving, and unethical as she attempts to achieve her ambitions. Other people are regarded with an eye to their potential usefulness and exist as pawns, to be controlled in a rather ruthless quest for achievement and power. The humanizing emotions of compassion, tenderness, and love find little place here. The clear and obvious identification for this type of woman is "Machiavellian."

Conceptualizations of the Schizophrenogenic Father.—Three different kinds of schizophrenogenic fathers were described by the 18 sorting psychiatrists. Again, these syndromes were sometimes employed separately and sometimes in combination in the various specific portrayals.

Before proceeding with the delineation of these three father types, it is pertinent to note that there was much less agreement among the sorters in describing the schizophrenogenic father than existed in the descriptions of the schizophrenogenic mothers. The average intercorrelation among the sorters for the father matrix was 0.16; the average correlation for the mother matrix was 0.32. The difference is a highly significant one and probably reflects the fact that psychiatrists have tended to focus their attention and reflection upon the mothers of schizophrenics, to the relative exclusion of the role of the father. There is another possibility that must be kept in mind, how-

ever. The fathers of schizophrenics may in reality be a more heterogeneous group, and, consequently, the relatively low agreements among sorters may be an expression of the different types of fathers with which each sorter has had experience.

The nature of the three father syndromes was ascertained by the same procedure employed with the mother sortings. Factor Q-sorts were contrasted with an average Q-sort compiled from the sortings of the 18 participating psychiatrists. Differences of two intervals were considered as defining.

For Factor X, the following statements proved discriminating.

Items Relatively Characteristic of the Factor-X Syndrome

Item No.

- 7 Favors conservative values in a variety of areas.
- 22 Feels separate, unconnected; feels a lack of personal meaning.
- 40 Is vulnerable to real or fancied threat; generally fearful; is a worrier.
- 46 Behaves considerably toward others.
- 59 Is concerned with his own body and the adequacy of its physiological functioning; aware of his bodily functions.
- 70 Behaves in an ethically consistent manner.
- 77 Appears straightforward, forthright, candid in dealings with others.
- 78 Follows routine in living; is orderly.
- 79 Tends to ruminate and have obsessive thoughts.
- 100 Does not vary roles; relates to everyone in the same way.
- 101 Arouses parental feelings in others.
- 107 Satisfied with his self; is not subjectively aware of self-concern. (N. B.: This refers to subjective satisfaction.)

Items Relatively Uncharacteristic of the Factor-X Syndrome

Item No.

- 13 Is original and imaginative. (N. B.: Quality of thought rather than quantity is to be emphasized.)
- 23 Tends to transfer blame.
- 36 Is subtly negativistic; tends to undermine and sabotage.
- 37 Is guileful and potentially deceitful.
- 38 Is sarcastic; cynical.
- 56 Is jealous; sees many potential rivals.
- 62 Tends to be rebellious and nonconforming.
- 69 Is sensitive to anything that can be construed as a demand.

- 71 Has high aspiration level for self; ambitious; wants to get ahead.
- 76 Tends to project his own feelings and motivations onto others.
- 89 Is envious; is overly alert to real or fancied differences between him and other people which he regards as placing him in an unfavorable light.
- 91 Is competitive.
- 92 Has social poise and presence; appears socially at ease.
- 98 Has conflicts about giving.
- 105 Characteristically pushes and tries to stretch limits; sees what he can get away with.

Comment: The above items portray the X-father as an introspective, obsessive, unhappy person, immobilized and without spontaneity. He is seen as an uncertain, passive, self-abasing person with a tremendous sense of failure. He has made a career of being a nonthreatening person, but his attempts to give and to relate to others would appear to be awkward, pathetic, and frequently misunderstood. This man is perhaps most appropriately characterized as the "defeated" father.

It is interesting to note that the conceptualization of the "defeated" father was offered usually by the psychiatrists who had also described the "Puritan" mother. In their eyes, schizophrenogenic parents are seen as jointly influencing the child. The dyadic relationship is seen as the "pathogen," not the additive effect of two separate relationships with the child.

The Factor-Y syndrome is described by the following items.

Items Relatively Characteristic of the Factor-Y Syndrome

Item No.

- 1 Critical, not easily impressed, skeptical.
- 7 Favors conservative values in a variety of areas.
- 9 Is intolerant of ambiguity.
- 24 Prides self on being "objective," rational.
- 48 Keeps people at a distance; avoids close interpersonal relationships.
- 51 Values intellectual and cognitive matters.
- 52 Behaves in an assertive fashion.
- 59 Is concerned with his own body and the adequacy of its physiological functioning; aware of his bodily functions.

- 61 Creates and exploits dependency in people; gives, but with strings attached.
- 63 Judges self and others in conventional terms, like "popularity," "the correct thing to do," social pressures, etc.
- 68 Emphasizes his personal privacy; prevents intrusion; secretive about his personal life.
- 69 Is sensitive to anything that can be construed as a demand.
- 71 Has high aspiration level for self; ambitious; wants to get ahead.
- 78 Follows routine in living; is orderly.
- 91 Is competitive.
- 93 Is masculine in his style and manner of behavior. (N. B.: This reflects the masculinity of behavior.)
- 96 Values his own independence and autonomy.
- 97 Has conflicts about receiving and being given to. (N. B.: If this item is placed toward uncharacteristic end of scale, it reflects the kind of person who "takes" excessively—seemingly without guilt or anxiety.)

Items Relatively Uncharacteristic of the Factor-Y Syndrome

- Item No.
- 2 Behaves in a self-abasing manner.
- 5 Behaves in an indulgent and forgiving way.
- 15 Is skilled in techniques of play, pretending, and humor.
- 35 Has warmth; has the capacity for close relationships.
- 42 Tends to delay or avoid action; fears committing self to any definite course of action.
- 43 Makes free use of facial expression and/or gesture in expressing himself.
- 58 Enjoys simple sensory experiences; likes touch, taste and smell; likes physical contact.
- 60 Has insight into his own motives and behavior.
- 65 Is able to sense other person's feelings; is an intuitive empathic person.
- 73 Makes many different contexts sexually relevant.
- 81 Is able to convey his personal feelings and inner thoughts.
- 83 Is genuinely sympathetic; compassionate for and with other people.
- 101 Arouses parental feelings in others.

The Y-father is conceptualized as a driving, aloof, impassive man, who is oriented toward what is efficient, orderly, predictable, and intellectual. There is an air of marked arrogance about him, and he evidences dis-

dain for those qualities in which he is most lacking—compassion, humility, playfulness, and the ability to be dependent on others. A cold, distant person, he seeks and thrives in competitive situations, where his drive to dominate, in conjunction with his suppression of feeling, can well prove to be ingredients for success. This type of father we have elected to call the "autocratic" father.

Factor Z is revealed by the following items.

Items Relatively Characteristic of the Factor-Z Syndrome

- Item No.
- 10 His anxiety and tension find outlet in bodily symptoms and dysfunction.
- 12 Tends to be self-defensive; anticipates being attacked and criticized.
- 34 Is irritable; overreactive to minor frustrations.
- 45 Has a brittle ego-defense system; has a small margin of integration; precarious self-control.
- 47 Has a readiness to feel guilty.
- 50 Is unpredictable and changeable in his behavior and attitudes.
- 53 His various needs tend toward relatively direct and uncontrolled expression; unable to delay gratification; acts out.
- 59 Is concerned with his own body and the adequacy of its physiological functioning; aware of his bodily functions.
- 62 Tends to be rebellious and nonconforming.
- 69 Is sensitive to anything that can be construed as a demand.
- 72 Concerned with own adequacy. (N. B.: This refers to a clinical judgment.)
- 74 Lets other people take advantage of him; allows exploitation.
- 80 Seeks out members of the opposite sex.
- 103 Thinks and associates to ideas in unusual ways; has unconventional thought processes.
- 106 Has anxiety.

Items Relatively Uncharacteristic of the Factor-Z Syndrome

- Item No.
- 3 Has a wide range of interests.
- 17 Behaves in a sympathetic manner.
- 18 Has a good sense of humor.
- 31 Would be organized and adaptive when under stress or trauma.
- 46 Behaves considerately toward others.
- 48 Keeps people at a distance; avoids close interpersonal relationships.

- 70 Behaves in an ethically consistant manner.
- 78 Follows routine in living; is orderly.
- 83 Is genuinely sympathetic; compassionate for and with other people.
- 95 Is generally counterphobic in his handling of fears, anxieties, and conflicts. (N. B.: Extreme placement of this toward uncharacteristic end of scale reflects a phobic reaction.)
- 96 Values his own independence and autonomy.
- 100 Does not vary roles; relates to everyone in the same way.

Comment: The Z-father is a chaotically organized, oscillating, anxious person, fitfully responding to the internal and external forces upon him. He allows exploitation of himself but is a rebel; he is self-defensive but is ready to feel guilty; he is inconsiderate and irritable with demands but seeks relatedness—in summary, an unadaptive, confused, contradictory, unsatisfied and unsatisfying, even adolescent, person. For convenience, this conception of the schizophrenogenic father may be referred to as the "chaotic" father.

A Limited Test of the Validity of Conceptualizations of the Schizophrenogenic Parent.—In the study previously mentioned in which the parents of 20 autistic children were contrasted with the parents of 20 neurotic children, the identical set of Q-items was employed to describe each participating mother and father.³ A battery of psychological tests provided the basis for the Q-sort formulations of each parent's personality.

A simple over-all test of the agreement of the conceptual sorts with the obtained data was provided by correlating each sort of the conceptualized schizophrenogenic parents with the sorts of the 40 actual parents. Theoretically, one would expect the conceptual sorts of the schizophrenogenic parent to correlate higher with the Q-sorts of the parents of schizophrenic children than with the Q-sorts of the parents of neurotic children.

These computations were performed for the conceptualized A-, B-, and C-types of schizophrenogenic mothers and for the X-, Y-, and Z-types of schizophrenogenic fa-

thers. For both mothers and fathers, there were no differences, or even trends toward differences, in the level of these correlations. In this study, then, and as evaluated from psychological tests, actual parents of schizophrenic children showed no greater similarity to the conceptualizations of the schizophrenogenic parent than did the parents of neurotic children.

However, a more refined analysis was then carried out. The Q-sorts of the 20 mothers of schizophrenic children and of the 20 mothers of neurotic children were intercorrelated and the resulting matrix analyzed, in an attempt to discern types of mothers within these groupings. One of the types derived consisted almost exclusively of the mothers of schizophrenic children, a result that statistically was not ascribable to chance. This type of mother, now identified as in some way etiologically relevant to the development of psychosis in her child, proved to be strikingly similar to both the A-mother, conceptualized by some psychiatrists, and to the C-mother, hypothesized by others. The correlation between the sorts of the A-, or puritanical, mother as conceptualized and the Q-sort typifying the subgroup of mothers of autistic children was 0.72; the correlation between the sorts of the C-, or Machiavellian, mother and the Q-sort typifying these mothers of schizophrenic children was 0.65. Both these figures are rather high. By way of comparison, the correlation of the sort of the B-, or "helpless," mother and the sort based upon actual mothers of autistic children is 0.09. These data suggest that two separate notions of the schizophrenogenic mother in combination have some validity, while another widely prevalent conceptualization is unrelated, at least in this first test, to the later development of autism in a child.

Although the same kind of more differentiated analysis was also applied to the Q-sorts of the fathers of these disturbed children, no positive results emerged. When categorized into subtypes, as in the over-

all analysis, the actual fathers of schizophrenic children evidenced no special similarity to any of the conceptualizations which have been offered.[†]

Comment

The results of this investigation provide some indication of the present state of agreement among well-known psychiatrists in regard to their conceptions of schizophrenogenic parents. There is a fair over-all agreement with respect to the character of the schizophrenogenic mother, although three diverging conceptions may be discerned. Understanding of the schizophrenogenic father has not progressed as far, if the general level of agreement among the participants is any indicator. Three kinds of schizophrenogenic fathers appear in the various conceptualizations, but the low level of agreement limits the significance of this finding.

In evaluating the import of the present study, three points appear to be worthy of emphasis. The first is that it is highly unlikely the results reported here would be changed to any appreciable degree by analyzing the conceptualizations of additional psychiatrists. Although there are many well-qualified persons with whom contact was not made for this study, all those who participated would unquestionably be recognized as competent, experienced, and highly interested in the question under evaluation. It is certainly fair to say that contemporary psychiatric opinion on the nature of schizophrenogenic parents is represented by the participants. Conceptualizations not here in-

cluded, be they proved more or less valid ultimately, are simply not part of the current psychiatric consensus.

The second point bearing emphasis expresses our conviction that the phenomenon of schizophrenia, in the child or in the adult, will prove to be more complexly caused than a universally applied conceptualization of the schizophrenogenic parent would imply. The finding in the present study, that two separate conceptualizations of the schizophrenogenic mother were, in combination, rather highly predictive of one kind of mother of the schizophrenic child, supports this contention. Although we give obeisance to the notion of multiple causation in psychiatry, too often observed relationships are phrased as unequivocal, even inexorable, ones, rather than as contingent upon a complex of factors.[‡] If the wisdom and insights accruing from clinical experience are to be recognized and used, the conditionality of these formulations will have to be respected.

Finally, the present study may be viewed as exemplifying a method which potentially has a larger application in psychiatry. A good many ambiguities and downright contradictions pervade the various definitions and usages of psychiatric terms. Such terms as "ego strength" and "hysteria" are utilized by the sophisticated as though there were general agreement as to their exact meaning. Frequently, issues of fundamental theoretical significance cannot be recognized because agreement between actually disparate views is assumed.

If only as a training device, the calibration of psychiatric concepts would appear to be a worth-while procedure. The Q-sort procedure, or some variant thereof, suggests itself as a convenient tool for the task be-

[†] It must be remembered that parents of schizophrenics are generally described implicitly vis-à-vis with the patient. Clinical experience suggests that the father may be a kind of counterpoint to the melody of the mother and thus not achieve significant form and substance in the clinician's mind. We have been unable to discover in the literature a single instance of a detailed clinical report of the psychotherapy of the father of a schizophrenic with a resultant dynamic description. Lidz' paper⁴ is the nearest approach to the problem; and, though a different methodology was used, the results are in close agreement with ours.

[‡] It is important to emphasize that the labels for the mother of "puritanical," "Machiavellian," or "helpless," are appropriate to the behaviorally descriptive level and do not necessarily imply a different pathologic relationship with the child. For example, the hypothesis developed by Bateson et al.¹ would fit all three types of mothers. Thus, "domination" or "helplessness" can have essentially the same effect on the child if the pathology is at a metacommunicative level.

cause it provides a quantifiable method of description in which differences in concepts become obvious. While there are some technical problems involved in the development of a suitable Q-set for a given context, with care these can be handled. Effective communication is no guarantor of progress in a science, but it is a precondition. It may be expected that the alignment of psychiatric concepts will permit a more direct approach to the substantive issues in the field.

Summary

A description of psychiatrists' conceptions of the "schizophrenogenic" parent is presented. Twenty psychiatrists, especially experienced and interested in the psychotherapy of schizophrenia, described their conceptions of the mother and the father of the schizophrenic by means of the Q-sort method. Three types of mothers were described.

1. The "puritanical" mother, an overly controlled, highly moral, and determined woman who brooks no interference with her concept of the world. She is relatively non-sensual and cannot tolerate ambiguity.

2. The "helpless" mother, a weak, anxious, and confused woman, who wants to be managed but has to sabotage the very control she requires.

3. The "Machiavellian" mother, who tends to be a manipulating and guileful person that clearly uses others in an attempt to attain power. She is devious, hostile, unfor-giving, and unethical.

Three types of fathers were also described, although the agreement among sorters was much less than that for mothers (0.32 as compared with 0.16).

1. The "defeated" father—an uncertain, passive, and self-abasing person, who is awkward and pathetic in his attempts to relate.

2. The "autocratic" father, a driving, aloof, and impassive man, who may be quite

successful but is a stranger to warm relationships.

3. The "chaotic" father, an anxious person who oscillates fitfully to the external and internal forces that impinge upon him.

The psychiatrists' conceptions were correlated with Q-sorts done on psychological data from the parents of schizophrenic children. Two mothers, the "puritanical" and the "Machiavellian," correlated highly, while the "helpless" mother and all of the father conceptions did not correlate in a statistically significant fashion.

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REFERENCES

1. Bateson, G.; Jackson, D. D.; Haley, J., and Weakland, J.: Toward a Communication Theory of Schizophrenia, *Behavioral Sc.* 1:251-264, 1956.
2. Block, J.: A Comparison of Forced and Unforced Q-Sorting Procedure, *Educ. Psychol. Measmt.* 16:481-493, 1956.
3. Block, J.; Block, J.; Patterson, V., and Jackson, D. D.: A Study of the Parents of Schizophrenic Children, *Psychiatry*, to be published.
4. Lidz, T.; Parker, B., and Cornelison, A. R.: Role of the Father in the Family Environment of the Schizophrenic Patient, *Am. J. Psychiat.* 113:126-132, 1956.
5. Sperling, M.: Psychosis and Psychosomatic Illness, *Internat. J. Psycho-Analysis* 36:320, 1955.
6. Stephenson, W.: *The Study of Behavior: Q-Technique and Its Methodology*, Chicago, University of Chicago Press, 1953.
7. Thurstone, L. L.: *Multiple-Factor Analysis*, Chicago, University of Chicago Press, 1947.
8. Jackson, D. D.: A Note on the Importance of Trauma in the Genesis of Schizophrenia, *Brief Communications, Psychiatry* 20:181-184, 1957.
9. Jackson, D. D.: The Question of Family Homeostasis, *Psychiatric Quart Supplement* 31:79-90 (Pt. 1) 1957.
10. Jackson, D. D., in discussion on Gavin, J.: The Mothers of Schizophrenics, read at a joint meeting of the West Coast Psychoanalytic Society and the Western District Branch Society of the American Psychiatric Association, San Francisco, 1955.

Effectiveness of Insulin Coma in the Treatment of Schizophrenia

A Control Study

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Introduction

The present study was undertaken in an effort to learn whether insulin coma therapy (ICT) per se had any effect in bringing about an improvement in cases of schizophrenia. This was an attempt to compare groups of truly similar patients in a setting where the only large variable would be the insulin itself. For this purpose it was necessary that all patients be placed directly in the insulin environment and subjected to the same procedures. The methods will be discussed later.

The literature concerning the validity of insulin coma therapy is extensive, and the variety of resulting conclusions about the problem is just as extensive. Investigators have concluded that ICT itself is of definite benefit in the treatment of schizophrenia,¹⁻³ that insulin coma is of no advantage,^{4,5} or that it may possibly be a detriment.

The inconsistency of these results may have resulted from one or more of several sources: The material studied has been collected from several hospitals with dissimilar diagnostic principles and dissimilar techniques and intensities of treatment.⁶ Selections of patients by several physicians may have given samples much farther from homogeneity than was desirable.⁷ Patients who were not reviewed by the same staffs for improvement or for discharge may have had to meet rather widely varying requirements, depending upon which doctors constituted the staff.⁷ Comparison of patients who underwent insulin therapy with those who had never been in an insulin unit may

not have revealed what effect the insulin itself had. This method omits a consideration of the environment. The intensive-treatment atmosphere, with small numbers of patients, a high personnel-patient ratio, and concrete visible forms of physical therapy, quite possibly acts on a psychosis in a different fashion than the usual hospital ward. The environments of various segments of the same hospital can be startlingly different. Patients in large studies were not known personally to investigators, and information about them obtained from records may have been inaccurate. Many studies reporting on success or failure of insulin show an average number of insulin treatments which is less than that number used in centers which report the most favorable statistics (30-50).⁶ Of those studies reporting a high number of insulin treatments, some reveal the patients to have been receiving doses which produced only light comas.

Studies covering 500 or 1000 cases are not in themselves any indication of statistical validity. Inferences drawn from a comparison of 1000 patients may be as erroneous as those from a comparison of 2 patients. The patients studied should be exposed to the same personnel, the same routine, the same building, the same medications. They should be selected by the same physician in every case and reviewed by the same staff in every case. They should arrive on the unit at the same time and should be seen at staff reviews at the same time. Their hospital experience should vary, within the controllable limits, only in the actual drug injected—insulin in one group, placebo in the other.

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A survey of the literature reveals almost no studies based on the above principles. There is extant a report of a comparative study of ICT and placebo-treated patients in which patients were matched and administered either isotonic saline or insulin.⁸ The results were slightly in favor of insulin-treated patients at the time of discharge and little different in follow-ups.

Of those investigators who have found a higher recovery in insulin-treated groups than in nontreated groups, many have ascribed this result to something in the intensive-therapy constellation other than insulin itself.⁹ Some postulate that the treatment situation enhances both the helplessness of the patient and the gratification of his needs (increased because of the coma state).¹⁰ It might be thought that the longer, more intensive human contacts would operate toward improvement.¹¹ Others have felt that physical treatment favors the establishment of affective relationships which facilitate forms of psychotherapy.¹²

The present investigation was constructed upon the hypothesis that the environment of insulin coma therapy is a more important factor than the insulin itself in promoting any differential improvement in treated over untreated groups. The opinion was that the patients in the insulin unit would improve in greater numbers than patients not treated there, but that both placebo-treated and insulin-treated groups would show this greater improvement and that there would be no significant difference between the groups on the unit.

Insulin Procedures

Selection of Patients.—The age limits for patients accepted to the unit are 20 to 45 years. At times exceptions are made so that patients younger than 20 or older than 45 are taken for therapy. Patients are free of any systemic illness. They are screened for heart disease, endocrine disorders (especially diabetes), and convulsive disorders. Psychiatrically, schizophrenics are preferred, especially the paranoid types. The more acute cases are taken in preference to chronic cases. The maximum number of patients on the unit is 10 male and 10 female subjects at any one time.

Treatment.—Insulin is administered by deep intramuscular injection at 6:00 a. m. Monday through Friday. Unmodified (amorphous) insulin is used, and this is stocked on the ward in units per cubic centimeter of 40, 100, and 500. During coma hours the patient's progress into coma is marked at 15-minute intervals on a sheet provided with the criteria of the stages. Patients generally have their coma terminated between 10:30 and 10:45 a. m. Termination of deep coma is by gavage or intravenous injection of 50% dextrose. Average doses of insulin range between 200 and 500 units daily.

Patients are given a concentrated sodium chloride tablet and a vitamin tablet daily. In addition, those patients prone to convulse in deep coma are placed on diphenylhydantoin sodium, grains 1½ (0.10 gm.) t. i. d. No other medications are given to insulin patients.

Unit.—The insulin unit is in a building one and one-half years old. The unit is self-contained, with its own treatment rooms and dormitories, and its own dining and recreation rooms. Insulin patients come in contact with other hospital patients only at weekly movies or dances. Insulin patients in general exhibit a solidarity of group feeling after they have been on the unit a short while. They seem to feel themselves apart from other patients and often regard other hospital patients with as much aversion as would a person unacquainted with psychotic patients and their behavior.

The unit is staffed with 3 nurses, 11 aides, and the unit doctor. The majority of personnel members are on the shift covering the coma hours. In addition to the hospital personnel, there are usually four to six student nurses in training on the unit at any one time. Although the students were changed frequently during the time of this study, all of the unit staff were on the unit from the beginning of the experiment until the end, without addition or withdrawal. All patients had the same doctor, nurses, and attendants during their stay on the unit.

Method of Study

Selection and Grouping of Patients.—Patients for the experimental insulin and placebo groups were selected according to the usual procedures of the unit described above. When admitted to the unit, patients were given a routine physical and laboratory check. Those patients unable to undergo insulin therapy for a physical reason were retransferred from the unit. This was necessary, since in any one case it was not known whether the patient was to be in the placebo or the insulin group. When the patient had been worked up completely, he was matched with another patient as closely as possible. In matching patients, the following criteria were used, in the order of importance indicated: type of schizophrenic reaction (i. e., paranoid, catatonic,

TABLE 1.—Admission Profiles

	Experimental Insulin Group	Placebo Group	Non- experimental Insulin Group
Average age	29.7 yr.	29 yr.	31.7 yr.
Age range	21-41 yr.	24-37 yr.	18-50 yr.
Paranoid	8	8	18
Catatonic	3	3	3
Undifferentiated	3	3	10
Other	0	0	1
First admission	11	11	22
Readmission	3	3	9
Average length of illness *			
Range	27 mo.	14 mo.	28 mo.
	3-45 mo.	1-36 mo.	
EST prev.	9	10	21
Chlorpromazine prev.	11	11	23
Insulin prev.	1	0	4
Total patients	14	14	32

* This does not refer specifically to hospitalization or treatment but refers to the time that symptoms were first noted.

undifferentiated schizophrenic); length of illness; first admission or readmission; age and sex, and type of previous treatment (i. e., ECT, tranquilizers, etc.). When a match was obtained, the pair was split, one patient going on one, and the other on the other, of the two lists. After the lists had been completed, they were submitted to a person outside the experimental setting, and he indicated one list as the insulin list and one list as the placebo list. Patients then were started on the treatment appropriate to their listing.

After the completion of the experiment the experimental insulin and placebo groups were matched in characteristics against the 32 patients from the previous year to see how they compared on admission with the average nonexperimental insulin patient. The admission profiles of all three groups are given in Table 1.

As can be seen from Table 1, the characteristics of the two experimental groups upon admission to the unit closely matched the profile of the usual insulin patient. This would be expected, since experimental patients were selected in the same fashion as the usual insulin patients. Since it was necessary to have matching pairs, the age range and the range of illness were narrower in the two experimental groups than in the usual insulin group.

In the admission profile there is a clearly discernible difference in the length of illness of the placebo patients. Since the patients were placed on the matching lists by a physician who had nothing to do with assignment of the lists to placebo or insulin, it seems that chance must have been the factor operating to bring this about. However the weighting occurred, it occurred in favor of the original hypothesis. This would serve to point out once again the strict caution necessary to ensure that there does not occur an unrecognized weighting in favor of a proposed hypothesis.

The Placebo.—Sterile water was chosen as the placebo. This was colored with from 2 to 10 drops

of phenolsulfonphthalein, depending on the supposed strength of the placebo. The bottles were labeled as U40, U100, or U500. The placebo was called "Spansulin" and was given the fictitious (and highly unlikely) chemical name of " β -(4-piperidyl) cupric hydrinsulin." "Spansulin" was a compound word created from "insulin" and "spansule," with the intent of promoting the idea of a long-acting insulin. Before instituting "Spansulin" therapy, the personnel were indoctrinated in the purpose and characteristics of "Spansulin." It was emphasized that the unit was participating in a test of a new long-acting insulin for insulin coma therapy. Emphasis was placed on the fact that no patient or relative should know of this. The personnel were told that, owing to the chemical composition of "Spansulin," the drug would be broken down in the body over a much longer period of time than regular insulin. In this fashion the patient would be enabled to have a coma dose of insulin without going into coma. If successful, this would cut down the incidence of complications in coma. It was further emphasized that the patients having this long-acting drug would have to be more closely watched for secondary reactions. Amounts of oral glucose and amounts of food intake at meals must be carefully regulated. Occasional group discussions of the drug were held throughout the course of the experiment with the personnel in order to answer questions about "Spansulin." By this underscoring of the possibility of long-delayed insulin reactions in the group of placebo patients, the attention of the personnel was continually directed toward them, even though the patients did not enter deep coma in treatment hours.

Treatment.—"Spansulin" patients were given a build-up course of treatment exactly following the dosage schedule for regular insulin patients. They received their injection at 6:00 a. m. and remained in bed in the treatment area until all deep comas had been terminated. Throughout the day, at the regular hour, they were given oral glucose in the same amounts as were regular insulin patients. On hot humid days it happened that patients would sweat profusely and be drowsy. When the personnel called this a Stage I coma, it was not corrected. The occurrence of such phenomena heightened the feeling that the "Spansulin" was truly insulin and so helped keep attention focused on the placebo patient.

Dosage.—The dosage of placebo was arbitrarily leveled off at 1000 units I. M. daily. This was later reduced to 500 units I. M. daily. The dosage of the insulin patients was maintained at the level necessary to give deep coma. It was necessary that all patients in the experiment be subjected to about the same length of time in the unit so that the environment could be said to be operating for the same duration in each case. In order to ac-

comply this, an arbitrary maximum of 71 treatments was drawn as the limiting factor of stay. The maximum allowed was based on study of regular insulin patients and their average number of treatments over a two-year span. This figure was found to be 71.8 treatments. In only one case was a patient allowed to go beyond this maximum number, and this patient received a total of 77 "Spansulin" treatments. Certain patients underwent improvement to the point of discharge before they reached 71 treatments, and these patients were not held on the unit to get the maximum number, but were discharged.

Staffing.—Once the maximum hours were reached, the patient was removed from therapy and "staffed." The patient was presented to two psychiatrists not working on the unit. His history was reviewed, but no estimate of improvement was given to them, and the type of therapy, whether "Spansulin" or insulin, was not revealed. The patient was then retransferred or discharged, according to the opinion of this small staff. Those patients discharged were considered treatment successes, and those patients transferred were considered treatment failures. The criteria of improvement will be listed below.

Rating Sheets.—At the beginning of the patient's stay on the unit he was rated by all personnel members. This was done on a simple 20-point questionnaire. The questionnaire covered the patient's appearance, speech, activities, and cooperation in ward routines. This rating was repeated during the course of treatment and, again, after treatments had been completed. In addition, at the end of the treatment span, all personnel members were asked to state in each case whether they felt the patient had improved and in what way; whether they felt the treatment was related to the improvement; whether they felt that the patient was well enough to go home, and whether they thought "Spansulin" or insulin was the better treatment. The primary purpose of these ratings was, again, to keep attention focused on the patients.

General Observations

This study lasted from October, 1956, through August, 1957, a period of 10 months. At all times there were three groups of patients on the unit: experimental insulin patients, "Spansulin" patients, and regular insulin patients not in either group being studied. Each group comprised about one-third of the unit. The total number of patients in the study was 28: 14 experimental insulin patients and 14 "Spansulin" patients. Characteristics of these patients

were compared after the experiment was finished with those of the 32 patients who either underwent deep coma therapy between April, 1956, and October, 1956, or were treated at the time the experiment was in progress. The statistics of these 32 patients are given only to see how closely the experimental groups would match any unselected sample of insulin patients. Larger groups perhaps would have been preferable, but to double the number of patients put through this experiment would have meant prolonging it close to another year. Since it is now felt that those patients given a placebo might have benefited by insulin treatment, such a delay would have meant depriving them of a valid treatment for from 6 to 18 months more.

It should be reemphasized here that the subjects were not drawn from comparable groups of patients and placed on either the placebo or the insulin list, but, rather, that matching of patients was done on a basis of individual for individual. When a patient

TABLE 2.—Comparison of Individual Patients

Diagnosis	Schizophrenic, paranoid Case 2A	Schizophrenic, paranoid Case 2B
Age, yr.	36	32
Sex	Female	Female
Hospital admission	First	First
Date admitted	10/8/55	5/12/55
Previous episodes	1954	1953
Previous therapy	EST; chlorpromazine	EST; chlorpromazine
Date admitted to unit	November, 1956	November, 1956
Experimental group	"Spansulin"	Insulin
	Case 6A	Case 6B
Age, yr.	26	26
Sex	Male	Male
Hospital admission	Second	Second
Date admitted	12/12/56	4/3/57
Previous episodes	May, 1955	September, 1955
Previous therapy	EST; chlorpromazine	EST; chlorpromazine
Date admitted to unit	April, 1957	April, 1957
Experimental group	"Spansulin"	Insulin

was recommended for insulin therapy, he was interviewed in his own ward. The patient's record was reviewed. A search was then made of the other recommended patients in order to see if a matching patient existed. Two samples of such matched pairs are listed in Table 2.

During the period of the initial work-up, and through the build-up phase, the groups were not demarcated in any definite way. There usually seem to be several weeks during which the patients become less disheveled, more presentable, and somewhat more amenable to ward procedures. These groups were no exception.

The majority of patients showed consistent weight gains for the first four weeks (20 treatments). The insulin group generally had higher average gains, but there was little consistency from patient to patient and during this period the insulin seemed to be showing no effect over the environment. By the time the second 20 treatments were started, however, differences began to be noticeable. The weight gains of the "Spansulin" patients leveled off, while the weight gains of the insulin patients continued their abrupt climb until therapy was concluded.

Reactions.—Both primary reactions (coma) and secondary (delayed) reactions are, of course, expected in insulin-treated patients. However, the appearance of these in placebo patients was surprising at first glance. Most placebo patients underwent at least 45 minutes of a light coma sometime during their course of treatment, and most of them suffered several delayed reactions. These comas were of Stage I variety, with sweating, muscle relaxation, and clouding of consciousness. No placebo patient went into a substantiated deep coma. The appearance of the light coma can be explained on the basis of a hypoglycemia occurring after a fast of some 10 hours. (Patients receive no food between evening of one day and lunch time of the next.) The added stress of the hypodermic injection and the sounds of an insulin-treatment dormitory during coma

hours perhaps served to increase the hypoglycemia even further and thus promote a sleepy, faint, perspiring state.

These reactions occurred chiefly during the first several weeks of treatment but tended to disappear as the patients became more acclimated to the insulin routine and more sophisticated about insulin coma. Again, in this area differences became more pronounced as the course of treatment progressed.

By the end of 20 treatments 11 insulin patients were leaving the hospital for weekend visits, while only 6 "Spansulin" patients had reached this point. Help on the wards generally came from the insulin group, although there were exceptions to this. Recoveries of patients occurred as early as the 50th treatment in both groups, although the average patient recovering required close to the arbitrary maximum of 71.

Periodic ratings by personnel showed that a majority of the insulin staff felt that the insulin group made consistently greater improvement gains than did the "Spansulin" group. Interestingly enough, the majority of personnel members rated the same patients improved as did the doctors at the time of staff evaluation. As the course of treatments went on, the unit personnel workers became unanimous in their preference for insulin as a treatment. This was despite the fact that in the beginning they had hoped the "new drug" would enable them to be under less of a strain during treatment hours. In their comments, they revealed the belief that the coma itself was the major factor operating in the widen-

TABLE 3.—Treatment Profile

	Exper. Insulin	"Spansulin"
Ave. weight gain	27.7 lb.	8.0 lb.
Range	16.5-43 lb.	-3.5 to +29.5 lb.
Ave. coma hours	67.8* subcoma 14 deep coma	0.9 subcoma 0 deep coma
Ave. no. of treatments	63	68
Range	50-71	50-71 *
Ave. length of stay	21 wk.	22 wk.

* In one case, 77 treatments.

ing difference between the two groups. At no time did it appear that the information that this new drug was actually a placebo had leaked to the staff or patients. The fact that any experiment at all was in progress was successfully hidden from the patients. Upon completion of treatment in the 28 selected patients, the personnel workers were informed of the nature of "Spansulin." Their reactions to this news were a fair indication of a complete lack of knowledge of the true composition of "Spansulin."

Results

The absolute standard of treatment outcome for the patients was discharge by the staff (success) or transfer to another service with discharge denied (failure). In considering whether a patient was ready for discharge, the following criteria were used: (1) freedom from major admitting signs and symptoms; (2) ability of patient to return to his previous social level; (3) ability of patient to return to an occupation previously held by him.

Patients who fulfilled all three criteria were considered as "recovered" of their psychotic episode. Patients were considered as in "remission" or as "much improved" if they had remaining minor signs, such as shallowness or flatness of affect, excessive shyness, etc., but were able to satisfy fully the second and third criteria. Patients who showed minor signs and who were unable to fulfill the second and third criteria were considered "improved," and those who fulfilled none of the criteria were considered "unimproved." Those patients who were discharged from the hospital (success) were

TABLE 4.—Discharge Criteria

Category	Recovered	Much Improved	Improved	Unimproved
Signs and symptoms	None	Minor	Minor	Major
Return to previous social level	Able	Able	Unable in one or both	Unable
Return to previous occupation	Able	Able		Unable
Disposition	Discharge	Discharge	Transfer	Transfer

TABLE 5.—Discharge Profile

	Exper. Insulin Group	"Spansulin" Group	Usual Insulin Group *
Discharged and remaining out of hospital	9 (64.3%)	4 (28.6%)	20 (62.4%)
Transferred or returned to hospital	5 (35.7%)	10 (71.4%)	12 (37.6%)
Total	14 (100%)	14 (100%)	32 (100%)

* For comparison.

in the "recovered" or "much improved" class only. Patients in the "improved" or "unimproved" category were transferred (treatment failure).

In ordinary circumstances some patients in the "improved" class might be taken home to become "family invalids." To do this, however, necessitates trying to judge what part treatment has played in improvement against that part the attitude of the patient's family might have taken. Obviously, some families will tolerate a patient with a major psychotic process still acting, while other families will exhibit standards for improvement more rigid than those adopted for the purposes of this investigation. Under the criteria listed above, the disposition of the patients shown in Table 5 was made.

Figures have varied widely for discharge rates among untreated schizophrenics. Much, of course, depends upon the hospital and its staffing. However, the placebo-group rate of success (28.6%) is in the range of discharge usually noted for the schizophrenic classification (22.0% to 35.1%).^{1,13} On the other hand, the experimental insulin group has a rate of success which is more than double that of the placebo group. Moreover, there is no real difference of success rate between the experimental insulin group (64.3%) and the usual average for insulin-treated patients in this unit (62.4%).

The differential in the figures for experimental insulin as contrasted with "Spansulin" can be attributed in large part to the action of the drug itself. This is further borne out by the close agreement between the two insulin group recovery rates.

Figures for the various subclassifications of schizophrenia have not been given because of the smallness of each group when treated this way. Nor have the transferred patients been separated from those discharged and returned for the same reason. Those patients discharged and remaining away from the hospital have been maintaining themselves for periods ranging from eight months to two months at the time of final revision of this report (October, 1957).

Conclusion

These patients were treated in a more intense setting than is usually reported. They received more treatments, and in heavier doses, and their stay on insulin was longer. However, a study of insulin patients in an environment of even greater intensity has been reported.¹⁴ The indications in this report were that insulin therapy has a positive value.

The evidence here is quite suggestive that insulin coma therapy itself is effective in the treatment of schizophrenia. Certainly these findings should be considered as an indication for the continued use of insulin coma as a therapy. They involve only a limited number of patients, and investigations of a similar type elsewhere would be of great value.

A second phase of this project is contemplated wherein former placebo patients will be returned to the insulin unit to receive regular insulin therapy. The recovery rate in this placebo group under insulin coma therapy may help validate or invalidate the present findings.

In addition, follow-up studies are necessary. The ultimate outcome (reflected, for example, in the two-year prognosis) remains unknown. Reports in the past have indicated that the ultimate prognosis is little different for insulin-treated patients than it is for the nontreated groups.^{3,10}

Summary

A study has been made of matched pairs of schizophrenic patients involving the use of insulin and of a placebo injection.

The patients for both groups were selected in the usual fashion for this insulin unit and compared for age, sex, length and type of illness, and previous treatment.

One of each pair was given insulin and one a placebo which had been previously described to the personnel involved as a new type of long-acting insulin called "Spansulin."

Both groups of patients were treated in the same place over the same periods of time, and both groups underwent identical routines except for the actual injection.

The criterion of successful treatment was discharge, and that of unsuccessful treatment, transfer.

The final outcome revealed that 64.3% of experimental insulin patients were discharged, but only 28.6% of placebo patients. These figures were compared with the usual discharge rate of this unit, which was found to be 62.4%.

The results indicate that insulin coma therapy is of positive benefit in the treatment of schizophrenia and, unless further work indicates otherwise, that it should remain in the psychiatric armamentarium.

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REFERENCES

1. Malzberg, B.: Outcome of Insulin Treatment of 1000 Patients with Dementia Praecox, *Psychiat. Quart.* 12:528-553, 1938.
2. Lewis, N. D. C.: What's What About Shock Therapy, *Ment. Hyg.* 30:177-185, 1946.
3. Bond, E. D.: Results of Psychiatric Treatments with a Control Series: 25-Year Study, *Am. J. Psychiat.* 110:561-566, 1954.
4. Taylor, J. A., and von Salzen, C. F.: Prognosis in Dementia Praecox, *Psychiat. Quart.* 12: 576-582, 1938.
5. Gottlieb, J. S., and Huston, P. E.: Treatment of Schizophrenia: Follow-Up Results in Cases of Insulin Shock Therapy and in Control Cases, *Arch. Neurol. & Psychiat.* 49:266-271, 1943.
6. Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments, Psychosurgery and Other Somatic Treatments in Psychiatry, Ed. 2, New York, Grune & Stratton, Inc., 1952.
7. David, H. P.: A Critique of Psychiatric and Psychological Research on Insulin Treatment in Schizophrenia, *Am. J. Psychiat.* 110:774-776, 1954.

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8. Notkin, J.; Niles, C. E.; DeNatale, F. J., and Wittman, G.: Comparative Studies of Hypoglycemic Shock Therapy and Control Observations of Schizophrenic Patients, *Am. J. Psychiat.* 96: 681-688, 1939.
9. Gralnick, A.: A 7 Year Survey of Insulin Treatment in Schizophrenia, *Am. J. Psychiat.* 101: 449-452, 1945.
10. West, F. H.; Bond, E. D.; Shurley, J. T.; Meyers, C. D.: Insulin Coma Therapy in Schizophrenia: A 14-Year Follow-Up Study, *Am. J. Psychiat.* 111:583-589, 1955.
11. Gershman, H.: Psychological Factors in Shock Therapy, *Psychiat. Quart.* 24:300-308, 1950.
12. Gottlieb, J. S., and Huston, P. E.: Treatment of Schizophrenia: A Comparison of Three Methods; Brief Psychotherapy, Insulin Coma, and Electric Shock, *J. Nerv. & Ment. Dis.* 113:237, 1951.
13. Hunt, R. C.; Feldman, H., and Fiero, R. P.: "Spontaneous" Remissions in Dementia Praecox, *Psychiat. Quart.* 12:415-425, 1938.
14. Brannon, E. P.; Graham, W. L.: Intensive Insulin Shock Therapy—A 5-Year Survey, *Am. J. Psychiat.* 111:659-663, 1955.

Chlorpromazine and Communication Processes

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Introduction

The favorable results that have been attributed to ataractic drugs in the treatment of chronic schizophrenic patients have led to numerous investigations to determine the psychological action of these agents. "Objective" studies designed to assess psychological effects occurring with such drug therapy have demonstrated few significant changes. "Subjective" clinical methods commonly employed are vulnerable to bias, as shown by Feldman.³ Some reported results are open to question because of faulty experimental design. As an applicable research design, the "double-blind" approach has important shortcomings, most noteworthy of which is that the investigator is seldom unaware of the drug group. Hall and Dunlap,⁵ using a double-blind approach, administered chlorpromazine in individually determined doses, up to 600 mg. daily, to a large number of semidisturbed schizophrenic patients and found significant improvement at the 5% level on subjective ratings by psychiatrists and a psychologist. However, agreement between raters was attained only 59% of the time, improvement was considered slight, and the authors felt that certain features of the experimental design (principally the method of coding the drug) and the side-effects (neurotoxicity incidence of 40%) detracted from the significance of their findings. The authors also emphasized that better control methods were desirable in view of the fact that 18% of the control

group showed improvement similar to the drug group.

Purpose

One of the most widely and successfully used tranquilizing drugs, chlorpromazine, has been assumed to facilitate psychotherapeutic processes by making patients more "accessible." This has been defined in a more limited way as an improvement in "communication" by Kinross-Wright⁶ and Pollack.⁹ The purpose of this experiment was to attempt to evaluate the effect of chlorpromazine on communication processes by means of objective psychological test techniques, recorded standardized psychiatric interviews, a sociometric study, and cinematographic samplings of spontaneous behavior in a relatively unstructured situation. Additional reasons for the inclusion of several test procedures outside the area of communication will be explained.

Procedure

Thirty-four chronic schizophrenic female patients without appreciable evidence of organic brain pathology were selected from the general patient population of the Galesburg State Research Hospital according to the following criteria: (1) cooperativeness on psychological testing and toward oral medication, (2) absence of any tranquilizing drug therapy for at least six months, and (3) competence with the English language.

Patients selected for the study were transferred to the same ward for more effective control of incidental environmental factors. Current activity participation and pass privileges remained unchanged. The drug and placebo tablets were provided and coded by the pharmaceutical company, and the code, sealed in an envelope, was kept at the hospital pharmacy until the completion of the experiment. Ward administration was assigned to a physician not involved in the project, and careful control of information about the experimental subjects was imposed to ensure against bias on

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From the Galesburg State Research Hospital. Henry Staras, M.D., gave assistance in the investigation.

Smith, Kline & French Laboratories, Philadelphia, supplied and coded the chlorpromazine and placebo used in this study.

CHLORPROMAZINE AND COMMUNICATION PROCESSES

TABLE 1.—*Descriptive Characteristics of the Experimental and Control Groups*

Group	Age		Hosp. Duration		Education		I. Q.	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean
A	45-74	63.75	4-30	17.92	4-12	8.18	75-104	91.27
B	49-65	58.64	6-29	16.09	6-16	10.27	68-115	92.60
C	45-72	61.00	8-39	21.91	3-13	8.18	76-101	89.80

the part of the investigators. The ward physician randomly assigned the patients to three groups. Group A consisted of 12 subjects; Groups B and C, of 11 each. Mean age, years in hospital, and I. Q. of each group are shown in Table 1.

The distribution of diagnoses for patients in each group is given in Table 2.

After a four-week period was allowed to patients on the new ward for adaptation, the experiment began. A uniform dose of chlorpromazine, 200 mg. at bedtime, was prescribed by the ward physician at six-week intervals, according to the schedule shown in Table 3.

The dosage was determined empirically to minimize sedative or other side-effects without sacrificing the desired therapeutic effect. Even so, transient neurotoxicity occurred in two cases. The placebo furnished was identical with the drug tablet so that all ward personnel would be unaware of the group on medication and less likely to treat them differently.

All patients were evaluated before the experiment began and after each of the six-week intervals (three times in all). The following procedures were employed.

A. Psychological Tests.—The tests utilized and the functions they were assumed to measure were as follows:

1. Wechsler-Bellevue Vocabulary subtest, Form I,¹⁶ split half: verbal intellectual functioning. The split half-form has been shown by Finkelstein et al.⁴ to correlate highly with total vocabulary score.
2. Ammons' Picture Vocabulary test¹: non-verbal intellectual functioning.
3. Kent-Rosanoff Word Association test (W-A). Fifty words were chosen from O'Connor's norms,⁷ which give the highest simple frequencies, and these were scored for (a) average response (Sc)—commu-

nality of response; (b) time per response under 10 seconds (T/R)—response latency; (c) number of blockings for 10 seconds or longer (BI)—response inhibition; (d) responses closely similar to the stimulus word (S)—close categorical association; (e) responses classified opposite the stimulus word (O)—tendency to pair words; (f) responses in the general category of the stimulus word (C)—variable relevancy; (g) responses considered irrelevant to the stimulus word (A)—response autism.

4. Word Naming: verbal fluency. This test was taken from the Stanford-Binet Scale¹⁴ and administered and scored according to directions in the manual.
5. Controlled Association: verbal fluency. The task consisted of writing as many four-letter words as possible, beginning with A, B and C, in a three-minute period.
6. First Digits Cancellation test: speed of recognition of numerical symbols. The subject was instructed to cancel all numbers in each row on a page identical with the encircled number preceding the row.²
7. Weight Suggestion test: a measure of suggestibility. The observation that patients undergoing pharmacological treatment are more amenable to psychotherapy carries the implication that they might be suggestible. The test was administered and scored according to the directions given by Thurstone.¹⁵
8. Tapping I: manual motor speed. The subject was asked to tap as fast as possible with a stylus on a metal plate attached to a counter for a 10-second period. This test was included to investigate possible changes in motor speed. Shatin et al.¹⁰ failed to find significant improvement on a similar test with chlorpromazine.

TABLE 2.—*Distribution of Diagnosis in the Experimental Groups*

Diagnosis	Group		
	A	B	C
Paranoid	5	2	3
Chronic undifferentiated	4	2	5
Hebephrenic	2	6	3
Schizoaffective	1	0	0
Simple	0	1	0

TABLE 3.—*Medication Schedule*

Group	Medication Schedule	
	0-6 Weeks	6-12 Weeks
A	Chlorpromazine	Placebo
B	Placebo	Chlorpromazine
C	Placebo	Placebo

9. Tapping II: hand-arm motor speed. The procedure was the same as above except that tapping alternated between two plates.
 10. Hidden Picture test. This test was adopted from a perceptual study by Thurstone.¹⁰ Discovery of acceptable figures is believed to require the ability to destroy a given gestalt in order to perceive a less dominant one. Identification of illusory figures was also scored. The test was used at this hospital in an unpublished study on intellectual deficit, and earlier results suggested sensitivity to drug effects.
- B. Psychiatric Interviews.*—Each patient was given brief standardized psychiatric interviews at 0-, 6-, and 12-week intervals, which were recorded verbatim for objective analysis. The three records were then compared and scored for fluency, spontaneity, quantity of verbalization, affect, coherence, comprehension, relevance, and fantasy material.
- C. Sociometric Evaluation.*—All patients were assembled, provided with pencil and paper, and asked to write the name of the person in the group whom they liked most and the one they liked least. The latter request was dropped because many of the subjects refused to write a negative choice. The responses were classified as follows: (1) interactive (chose and was chosen); (2) social isolate (chose but not chosen); (3) self isolate (chosen but wouldn't choose); (4) total isolate (wouldn't choose and was not chosen).
- D. Cinematographic Record.*—Mixed groups of seven subjects each were ushered into a large, barren room equipped with a one-way mirror and instructed only that they would stay in the room for 10 minutes. Motion pictures were taken of their behavior as they entered the room and at intervals of 10 seconds every 2 minutes for the 10-minute period. This sampling of behavior was evaluated for changes in activity level, verbal interaction, autism, and self-interest (the mirror allowed for primping).

Results

When all data had been collected, the code was made known and test data and subjective ratings evaluated by *t*-test comparison of mean change between periods and analysis of changes in variance for each group between periods.

Statistical treatment of scores yielded some significant changes, but in general these

were scattered and provided no consistent interpretable pattern (Table 4).

The postdrug group had a significantly higher response latency on the Word Association test and a significantly faster Tapping I score. A suggestive interpretation, on the basis of slender evidence, might be that increased anxiety in Group A for the postdrug period of 6 to 12 weeks accounts for the delay in verbal response time. Together with the increase in simple tapping speed, these results are not inconsistent with Spence and Taylor's findings^{12,13} that anxiety facilitates simple conditioned responses and interferes with responses of a more complex nature. These results would also lend support to reported observations that the level of anxiety is reduced by chlorpromazine. However, the tenuousness of the above interpretations is reflected in the fact the controls showed other changes in the same direction as the drug groups, or even in the absence of changes in the drug groups.

Using the initial recorded psychiatric interview as a basis for comparison, each subject was evaluated after six weeks on the eight variables described in (B), above. The second recording then became the basis for rating the third interview record. Ratings were made on a seven-point scale. Significant positive changes were found for the B drug group on "coherence." Inasmuch as such a trend also is noted in the controls after the first six weeks, approaching 0.10 probability, and is absent in the A drug group, any drug-effect interpretation would seem untenable. Postdrug Group A showed greater "relevance" while the controls moved in the direction of less relevance for the same time period. No meaningful interpretation of this finding in terms of drug effects seems warranted. On the remaining variables the pattern of mean differences was inconsistent, and similar changes occurred with the controls.

The McNemar test for the significance of changes¹¹ was applied to the sociometric responses. A plus score was given if the

CHLORPROMAZINE AND COMMUNICATION PROCESSES

TABLE 4.—Significance of Mean Differences Between Periods

Variable	Chlorpromazine		Postdrug		Placebo	
	A 6-9	B 13-16	A 13-16	B 6-9	C 13-16	C 6-9
Pict. vocab.	-0.08	0.73	3.17 *	4.73 †	1.64	2.09 ‡
Sugg. score	4.33	6.27 §	0.67	1.82	-2.64	5.82 ‡
Con. assoc.	1.42	0.91	0.27	2.18	(3.09)	0.09
First digits	1.50	-1.36	0.17	1.96	1.50	1.05
W-A score	13.92	7.00	-6.83	0.00	-1.91	4.18
T/R	-0.34	-0.06	0.13 §	-0.07	-0.01	(-0.25)
Bl	(-1.33)	-0.36	-0.33	(-1.00)	-0.73	-0.73
S	-0.26	-0.36	0.58	-0.27	0.09	-0.45
O	0.33	1.82	-1.92 §	0.27	-1.36	-0.36
C	3.83	1.64	3.00 §	(3.64)	2.91 ‡	2.64 §
A	-3.08	-3.09 ‡	-1.67	-3.55	-1.45	2.00
W-B vocab.	-0.58	0.55	1.29 †	0.54	-0.73	1.14 †
H. P. Real	0.50	0.73	0.17	0.82	3.54 §	-0.27
H. P. Imag.	1.00	3.09	(1.25)	0.64	(3.82)	(-2.00)
Tapping I		(5.82)	6.35 †			0.82
Tapping II		0.27	(5.75)			1.82
Word naming		-0.82	-3.50			-0.82
Fluency	-0.25	1.18	0.42	-0.42	0.27	-0.36
Spontaneity	-0.08	1.18	-0.17	-0.64	0.18	-0.64
Quantity	0.25	0.73	0.00	-0.18	-0.09	-0.73
Affect	-0.50	1.18	0.08	-0.55	0.18	-1.09 ‡
Coherence	0.08	0.91 §	0.00	-0.27	0.36	-0.18
Comprehension	-0.08	1.10 §	0.08	-0.27	0.36	-0.82 §
Relevance	-0.42	0.55	0.58 ‡	-0.36	0.18	-1.00 §
Fantasy	-0.83 *	0.64	0.33	-0.42	-0.09	-0.91 §

* $P=0.01$.† $P=0.02$.‡ $P=0.05$.§ $P=0.10$.|| Parentheses indicate *t*-test values invalidated by variance changes. Blank spaces indicate absence of data during first evaluation period.

subject moved one or more steps in the direction of "social interaction"; a minus score, if movement was in the opposite direction. Again, no significant changes were found.

Motion picture behavior samples were evaluated for changes listed in (D), above. The initial sample on each patient was used as a basis for rating the second sample, and the second became a standard for the third rating. Ratings of "plus," "minus," or "no change" were made separately by the three investigators, and the numerical rating on a particular variable given by two of the three was accepted. Data were subjected to the same procedure as the sociometric ratings

and proved insignificant. Small χ^2 values obviated the necessity of examining rater reliability.

Conclusions

Chlorpromazine in the dosage used failed to show any effect on the communication processes evaluated here. Several considerations are in order in interpreting this absence of significant change. The widespread use of tranquilizing drugs made it difficult to locate experimental subjects who had not received some ataractic drug for a long enough period to ensure against possible sustained improvement from previous treatment. Furthermore, those chosen for the

study may have been patients who had not responded satisfactorily to drug therapy previously and had therefore been removed from treatment. Individually determined optimal doses may have more closely approximated maximum drug benefits but allowed less insurance against research bias because of probable side-effects. It is possible that our methods were insensitive to subtle changes, which may have occurred. Our measures were largely confined to overlearned behavior patterns, which are perhaps unaffected by chlorpromazine as prescribed. The evaluation of psychological changes with drug therapy by measuring efficiency in the learning of novel tasks and problem-solving activities, as suggested by Pearl⁸ might be a more rewarding approach.

The fact the placebo group improved when similar changes were evident in the drug groups or when such a trend was absent in the drug groups supports the assumption that an undefined, nonpharmacologic variable is exerting influence on the subjects. Since this experiment was relatively well controlled, one might hypothesize that the changes which occurred in a positive direction were due to practice effects (psychological tests) and/or increased attention. Perhaps the suggestive act of giving a tablet to a receptive patient may be of therapeutic value. It is interesting to note that some of the controls (C group) showed hysterical symptoms, i. e., fainting and dizziness, shortly after the experiment was initiated. There is some objective evidence that chlorpromazine effects a decrease in anxiety level. However, our results are only suggestive for further research.

Summary

The purpose of this study was to investigate the efficacy of chlorpromazine in facilitating communication processes. Thirty-four chronic schizophrenic patients were divided into three groups. Two groups received 200 mg. of the drug and placebo during alternate six-week periods, while the third group was a continuous control on placebo. The groups

were roughly equivalent for age, hospital duration, and I. Q. The drug and placebo tablets were coded by the manufacturer, and subjects were assigned at random to groups by a ward physician, so that the investigators and all ward personnel who worked with them were unaware of the drug groups. The group not on drug at a particular period, as well as the controls, received a placebo tablet identical with the drug. Initially and at two subsequent six-week intervals each subject was given various psychological tests, recorded psychiatric interviews, and sociometric evaluations, and cinematographic samplings of spontaneous behavior in a relatively unstructured situation were made. Data were subjected to statistical treatment for each evaluation method employed. Results failed to establish that 200 mg. of chlorpromazine, as prescribed, significantly alters communication processes as measured here, but there is some evidence to support the observation that there is a reduction in anxiety with this drug. Possible explanations for the absence of positive results are discussed.

Galesburg State Research Hospital.

REFERENCES

1. Ammons, R. B., and Ammons, H. S.: Full Range Picture Vocabulary Test, Louisville, Ky., Psychological Test Specialists, 1948.
2. Becktoldt, H. P.: A Factorial Investigation of the Perceptual Speed Factor, *Am. Psychologist* 2:304-305, 1947.
3. Feldman, P. R.: The Personal Element in Psychiatric Research, *Am. J. Psychiat.* 113:52-54, 1956.
4. Finkelstein, M.; Gerboth, R., and Westerhold, R.: Standardization of a Short Form of the Wechsler Vocabulary Subtest, *J. Clin. Psychol.* 8:133-135, 1952.
5. Hall, R. A., and Dunlap, D. J.: A Study of Chlorpromazine: Methodology and Results with Semi-Disturbed Schizophrenics, *J. Nerv. & Ment. Dis.* 122:301-314, 1955.
6. Kinross-Wright, V.: Chlorpromazine Treatment of Mental Disorders, *Am. J. Psychiat.* 111: 907-912, 1955.
7. O'Connor, J.: *Born That Way*, Human Relation Series 7, Baltimore, Williams & Wilkins Company, 1928, pp. 225-310.

CHLORPROMAZINE AND COMMUNICATION PROCESSES

8. Pearl, D.: James Quinter Holsopp Memorial Symposium: Psychology and the Tranquilizing Drugs, read at the Annual Convention of the American Psychological Association, 1956.
9. Pollack, B.: Preliminary Report on 500 Patients Treated with Thorazine at Rochester State Hospital, *Psychiat. Quart.* 29:439-456, 1955.
10. Shatin, L.; Rockmore, L., and Funk, I. C.: Response of Psychiatric Patients to Massive Dosages of Thorazine: II. Psychological Test Performance and Comparative Drug Evaluation, *Psychiat. Quart.* 30:402-416, 1956.
11. Siegel, S.: *Nonparametric Statistics for the Behavioral Sciences* (McGraw-Hill Series in Psychology), New York, McGraw-Hill Book Company, Inc., 1956, pp. 63-67.
12. Spence, K. W., and Taylor, J.: Anxiety and Strength of the NCS as Determiners of the Amount of Eyelid Conditioning, *J. Exper. Psychol.* 42:183-188, 1951.
13. Taylor, J. A., and Spence, K. W.: The Relationship of Anxiety Level to Performance in Serial Learning, *J. Exper. Psychol.* 44:61-64, 1952.
14. Terman, L. M., and Merrill, M. A.: *Measuring Intelligence: A Guide to the Administration of the New Stanford-Binet Tests of Intelligence*, Boston, Houghton Mifflin Company, 1937, pp. 258-259.
15. Thurstone, L. L.: *A Factorial Study of Perception*, *Psychometric Monographs*, Vol. 4, pp. 81-83, 1944.
16. Wechsler, D.: *Measurement of Adult Intelligence*, Baltimore, Williams & Wilkins Company, 1944.

News and Comment

ANNOUNCEMENTS

First World Mental Health Year.—At its annual meeting in Copenhagen last summer, the World Federation for Mental Health designated 1960 as the First World Mental Health Year.

Mental Health Year will cover, as the IGY did, the 18-month period from Jan. 1, 1960, to June 30, 1961, and will culminate in the Fifth International Congress on Mental Health, to be held in Paris in August, 1961.

Preparatory work for the First World Mental Health Year is already under way. The 32 member associations in the United States will set up a common joint steering committee to guide the preparatory work and the United States' share in the common world-wide undertakings for 1960. In addition to the common undertakings, different countries will pursue special projects of their own choosing, designed, among other things, to reveal the status and needs of mental health in that country and to develop new resources.

The Executive Board of WFMH has established a committee to plan for the First World Mental Health Year, the initial members of which are Dr. Frank Fremont-Smith, of the United States, chairman; Dr. John R. Rees, ex-officio, of England; Dr. Brock Chisholm, of Canada, and Dr. Paul Sivadon, of Paris.

Information on the United States' effort may be obtained from the U. S. Office of the Federation: 10 Columbus Circle, New York 19.

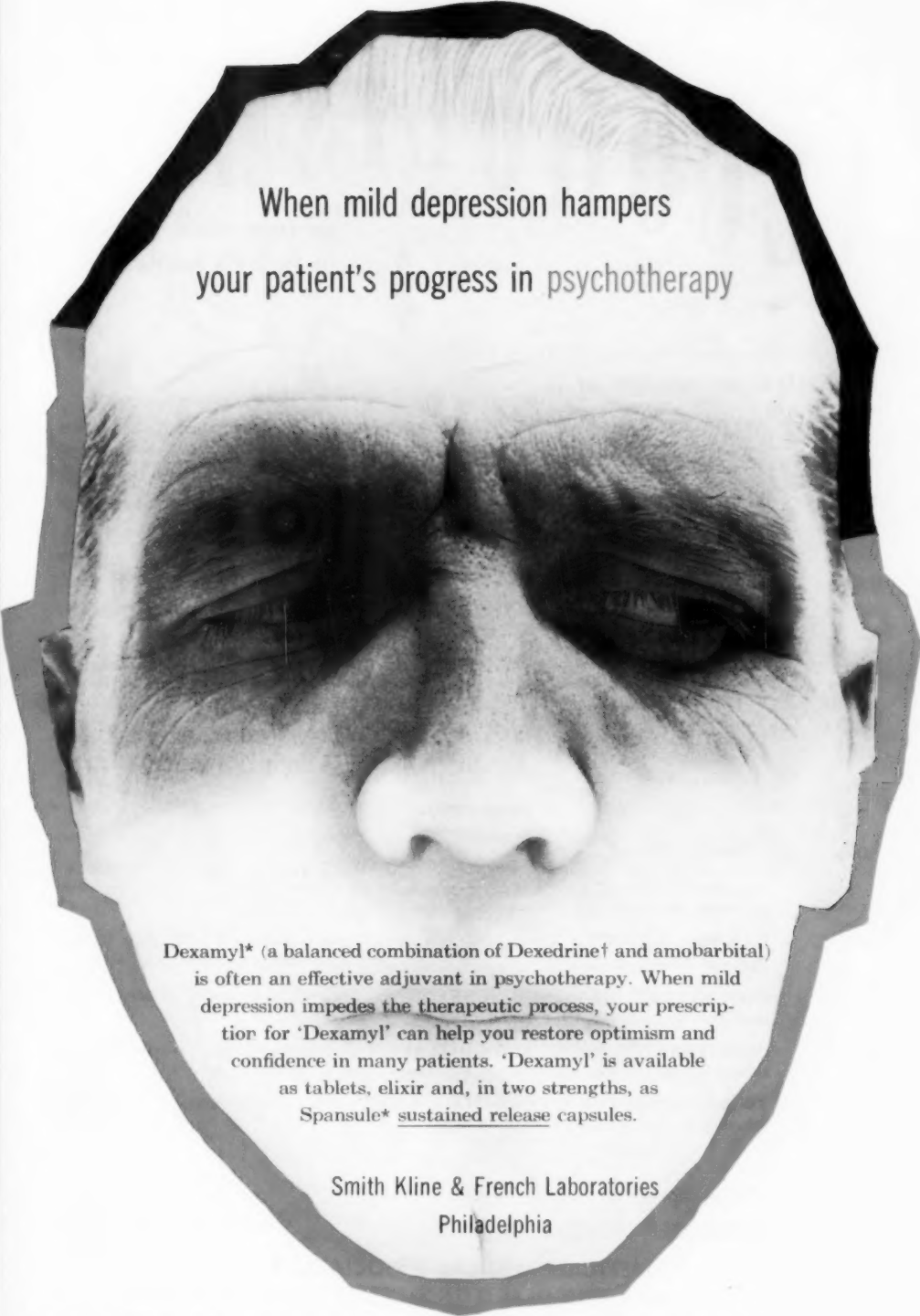
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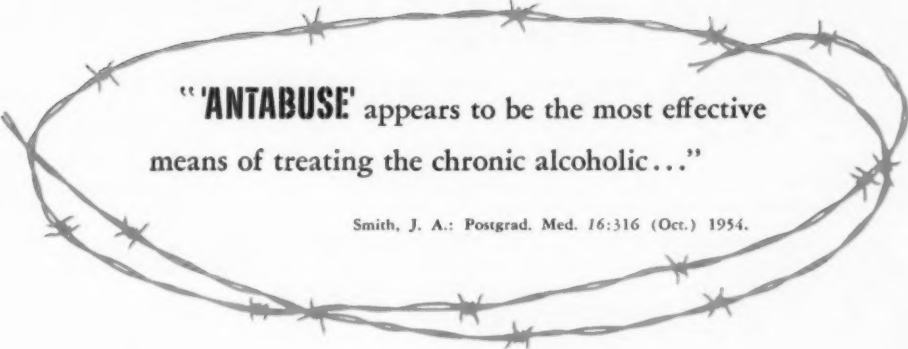
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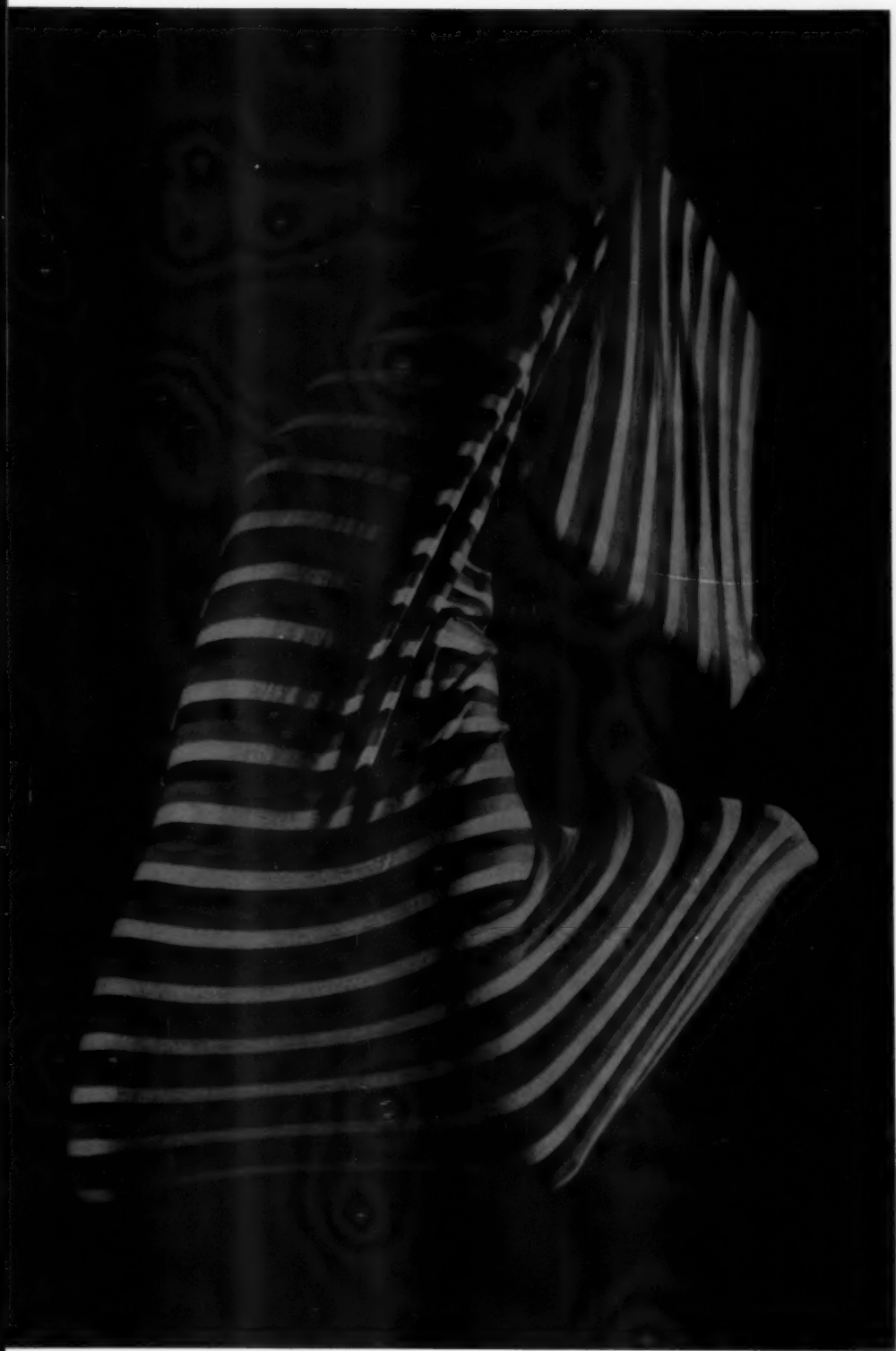
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Goldman, D.; Stephens, F.M.; Rosenberg, P., and Rosenberg, B.: Prochlorperazine in the Treatment of Psychiatric Patients, scientific exhibit, Clinical Meeting of the A.M.A., Philadelphia, December, 1957.

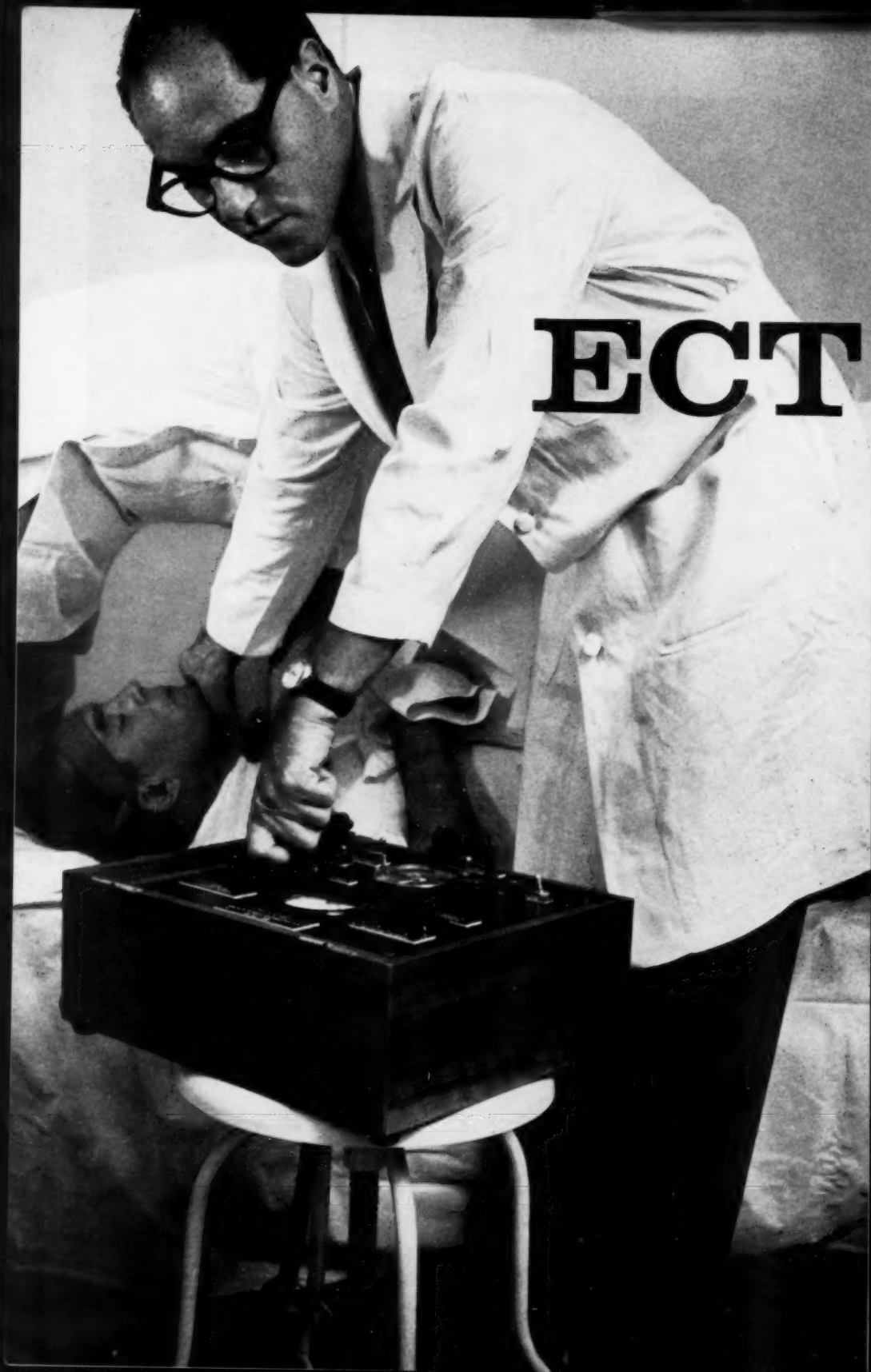
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*Alexander, L.: *Chemotherapy of depression—The use of meprobamate combined with 2-diethylaminoethyl benzilate hydrochloride (benactyzine)*. J.A.M.A. 166:1019, Mar. 1, 1958.

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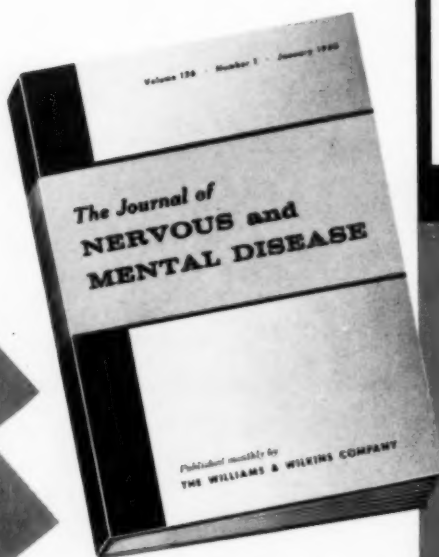
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Outstanding articles in the January, 1958, issue of the JOURNAL OF NERVOUS AND MENTAL DISEASE

THE NATURE OF APRAXIA

By D. Denny-Brown

One of our foremost clinicians brings together problems of neurology and psychology. Distinguishes between ideational and kinetic apraxia on the basis that the former is related to non-physiological aspects of behavior.

ON THE PARTICIPATION OF ADAPTIVE HORMONES IN DISEASE SUSCEPTIBILITY

By Hans Selye

The most recent contribution to the field of adaptability to stress by a pioneer in that important area.

THE SEVERELY DEFECTIVE INDIVIDUAL

By Seymour B. Sarason and Thomas Gladwin

A psychologist and anthropologist explore the relationship between psychoses and subnormal functioning. The first intensive study of this important area.

SOME ASPECTS OF AMINO ACID AND PROTEIN METABOLISM OF THE NERVOUS SYSTEM

By Dr. Heinrich Waelsch

Deals with metabolism of nitrogenous compounds in the central nervous system. Of primary interest not only because of the role of amino acids in the formation of proteins and active amines (such as noradrenalin, serotonin, etc.), but also because of their possible major activity in the mechanisms of storage and transmission of information.

A CATARACT OF CONSEQUENCES

By Alan Gregg

Read at the Dedication of the Psychiatric Institute, University of Maryland School of Medicine, Baltimore, 1952. This previously unpublished manuscript by Dr. Gregg is particularly appropriate to the inauguration of the new editorial policy of the Journal, in that it clearly reflects the multi-disciplinary point of view of this great educator.

Important papers read before the 1957 meeting of the Society of Biological Psychiatry . . .

Visceral Brain, Its Component Parts and Their Connections.

By James W. Papes

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